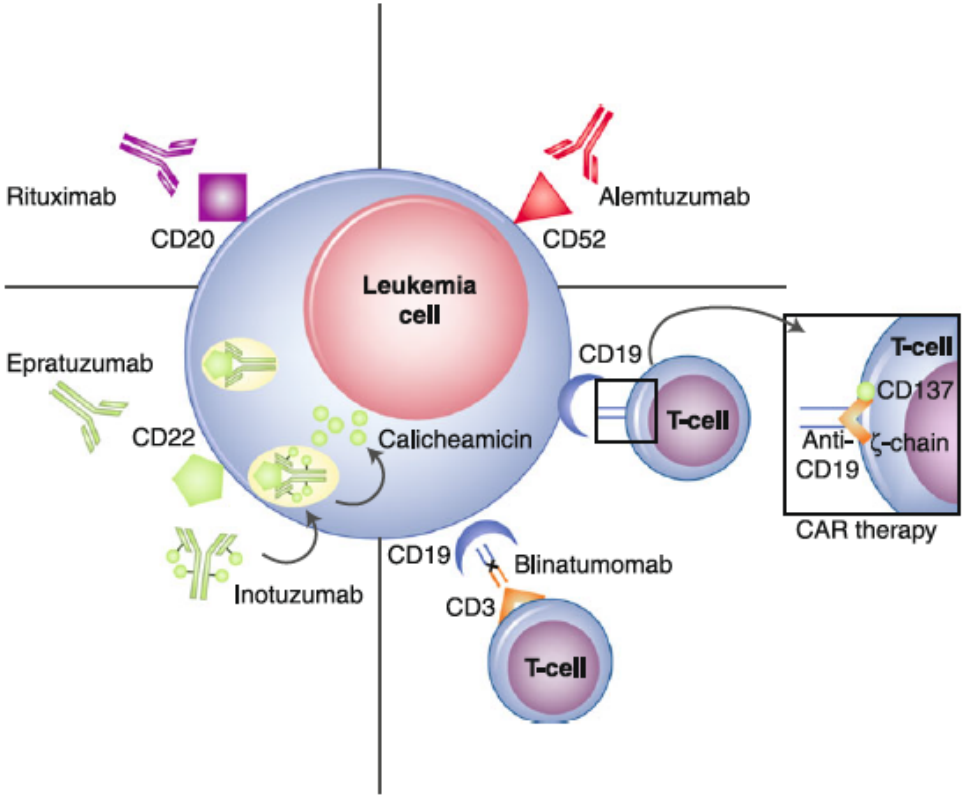
Immunotherapies in Acute Lymphoblastic Leukaemia

Professor David Ritchie
Royal Melbourne Hospital

The Royal Melbourne Hospital


Rituximab
CD20
Alemtuzumab
CD52
Leukemia cell
Epratuzumab
CD22
Calicheamicin
CD19
T-cell
T-cell
CD137
Anti-CD19
ζ-chain
CAR therapy
Inotuzumab
CD19
Blinatumomab
CD3
T-cell

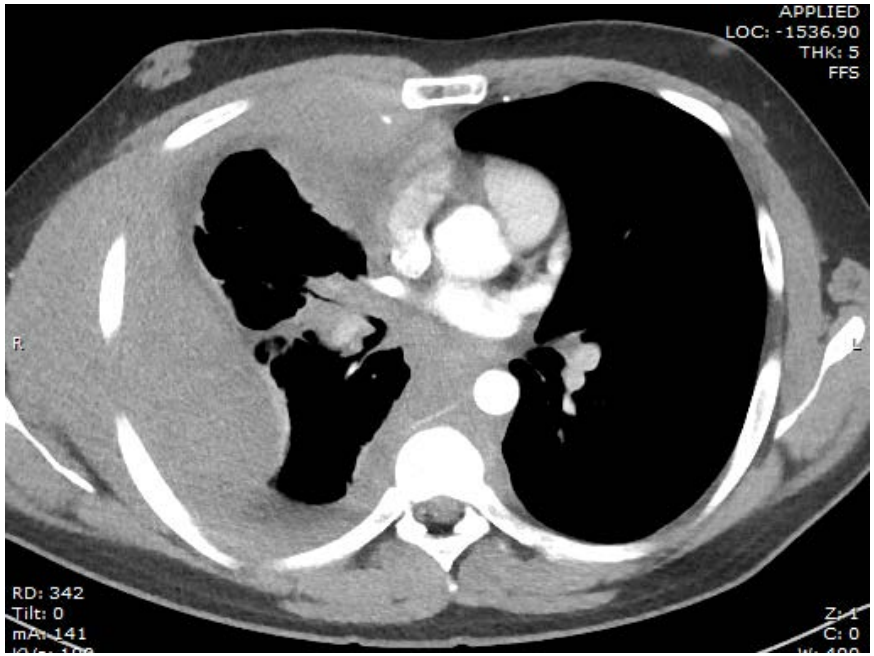
Blinatumomab Cases

Case 1: Mr BE

- 30 year old male
- Aged 17, diagnosed Philadelphia negative B-ALL in Nov 2004 - Chromosome 16 abnormality
- Commenced treatment with ALL VII paediatric protocol Dec 2004 – CR
- Aged 19, Relapse with 10% blasts on marrow with neutropenia and thrombocytopenia (August 2007)
- Etoposide/TBI sibling allogeneic stem cell transplant (Sept 2007)- CR
- Re-presented following trip to Sri Lanka with marked shortness of breath (July 2015).

Pleural fluid, lung and bone marrow biopsy confirm relapsed B-ALL

- No evidence of original chromosome 16 abnormality
- CD19+, CD20+, CD22+
- CSF negative for disease

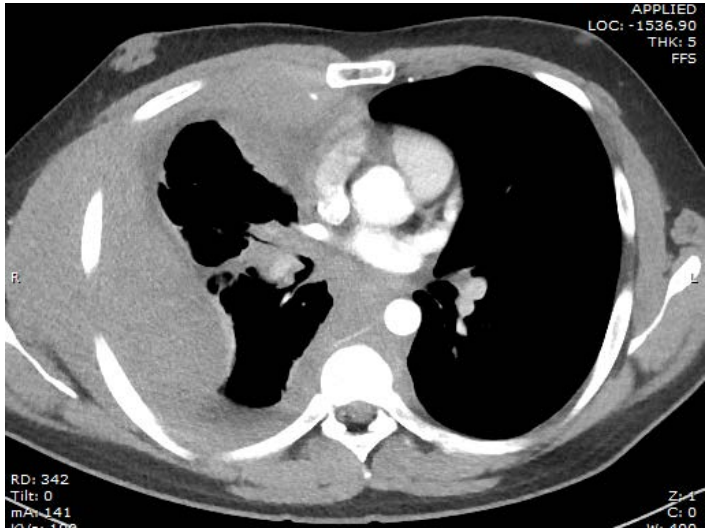


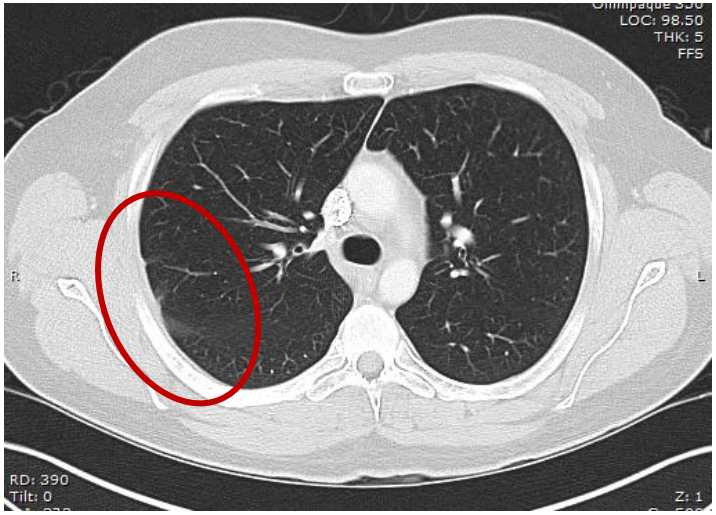
Commenced blinatumomab on TOWER study: July 2015

- Initial dosing complicated by cytokine release syndrome and rapid AF
  - Settled with steroids and spontaneous AF reversion
- Subsequent dose escalation complicated by:
  - Deranged LFTs – within 2 weeks post commencement
    - **ALP/GGT: 209/237;**
    - **ALT/AST 47/59;**
    - **Bili 10umol/L; INR 1.0**
    - Settled with steroids and dose reduction
  - Mental clouding/confusion and dysgraphia
    - Resolved with steroids and dose reduction
  - Concurrent mild neutropenia
    - Resolved with dose reduction
    - Neutrophils 1.8

Response to blinatumomab

- Post cycle 1 – 2.5% blasts in BM
- Post cycle 2 – 0% blasts, no MRD by flow
- Post cycle 8 (maintenance)
  - 0% blasts, no MRD by flow
- Normal LFTs
- Faint tenting of pleura on R) side
- Completed full protocol (9 cycles) in Dec 2016
- Ongoing CR.





Case 2: Ms LP

- 48 year old female
  - PMHx: hypertension, Grave's disease, retinal detachment, one pregnancy
- Diagnosed with Philadelphia negative B-ALL (June 2013)
  - High WCC (167), 89.5% blasts,
  - Multiple cytogenetic abnormalities: t(1;7), 13p-, abnormalities 6q, 11p, 11q, 18q,
- 6 cycles of HyperCVAD therapy
  - Post 1A - 5.5% blasts
  - Pre-allograft 0% blasts, 0.08-0/09% MRD by flow
- Etoposide/TBI/thymoglobulin matched unrelated donor allogeneic stem cell transplant (1^{st} transplant)
  - Complicated by cyclosporin-associated renal injury and hypertension
  - No GVHD.
  - MRD negative CR post alloSCT for 2 years.

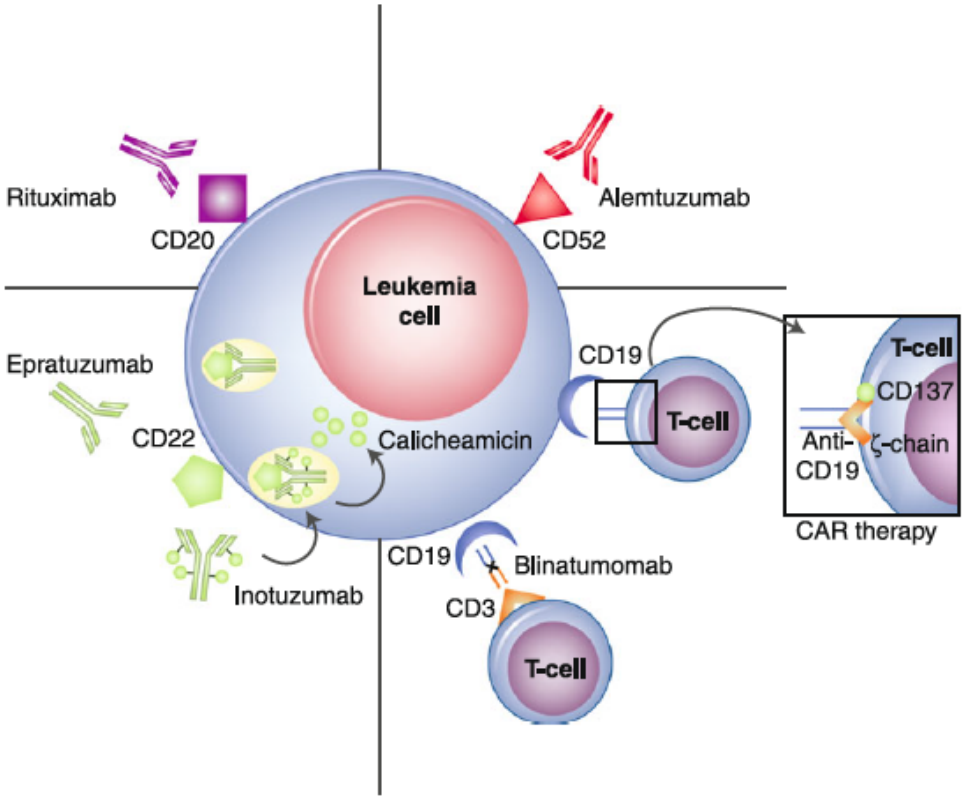
Relapse, blinatumomab, transplant, blinatumomab

- Blasts on peripheral film observed Oct 2015
  - Chimerism CD3+/- (%): 88/66
- BMAT confirmed relapsed disease
  - 87.5% blasts
  - Clonal evolution by cytogenetics: t(1;7), del(13q), 18q abnormality, new abnormalities in 11q, 12p and 12q
- Post cycle 1 blinatumomab
  - 5.5% blasts, persistent 13q abnormalities on FISH
- Post cycle 3 blinatumomab, pre 2nd alloSCT
  - 4% blasts, persistent 13q abnormalities on FISH
- Proceeded to 2nd alloSCT – same donor, bone marrow source (April 2016)
  - Fludarabine, low dose cyclophosphamide, no T cell depletion, planned rapid IS withdrawal.
    - Complicated by line sepsis, rapid AF, hypertension
    - Scheduled day 30 marrow

Blinatumomab post 2nd transplant

- Day 30 marrow
  - 10.5% blasts, persistent 13q abnormalities on FISH
  - Chimerism CD3+/- (%): 99/91
- Commenced blinatumomab June 2016
- Complicated by
  - Markedly deranged LFTs within 1 week of dose escalation
    - **ALP/GGT: 263/459;**
    - **ALT/AST 1065/539;**
    - **Bili 13umol/L; INR 0.9**
    - Dose with-held and then dose reduced
  - Neutropenia
    - Managed with cytokine support
- ***Post 2nd cycle BMAT showed no abnormal blast population by flow cytometry, and normal CG.***
- *Has now competed 6 cycles and remains in MRD neg CR.*

Immunotherapeutic option in Acute Lymphoblastic Leukaemia



MoABs
DAbCs
BiTEs
CAR-T

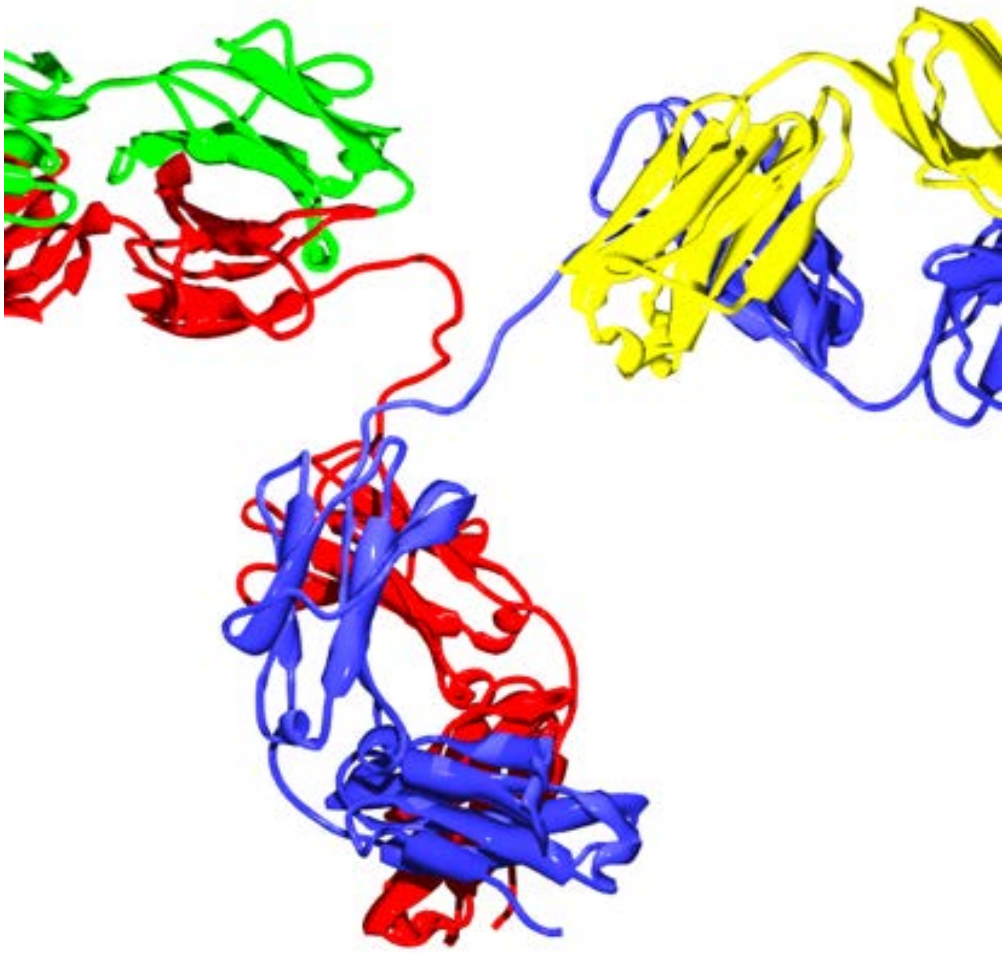
Spectrum of ALL

Classification	Immunophenotype
Precursor B-cell ALL	
▪ Pro-B ALL*	CD10-, CD19+, CD79a+, TdT+
▪ Pre-B ALL†	CD10+, CD19+, CD22+, CD79a+
T-cell ALL	Cytoplasmic or surface CD3, variable expression of CD1a, CD2, CD5, CD7, TdT, CD52

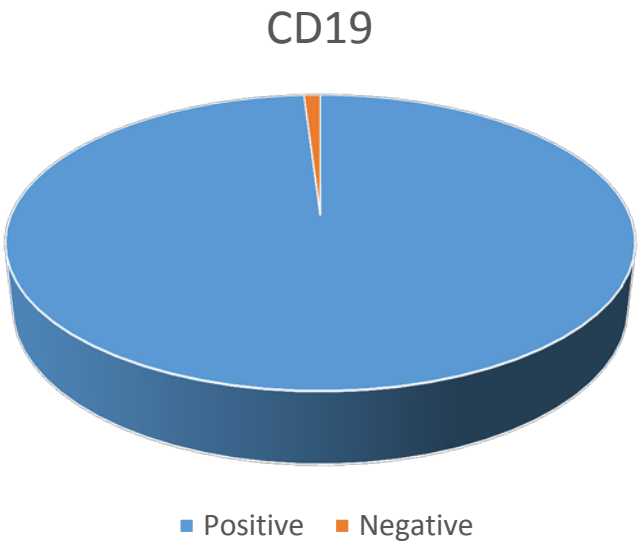
*Early precursor B-ALL.
†Previously called common B-cell ALL.

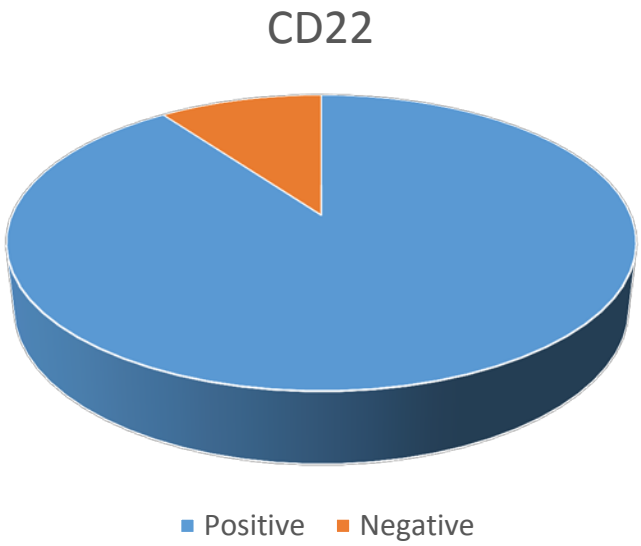
Immunotherapy in ALL

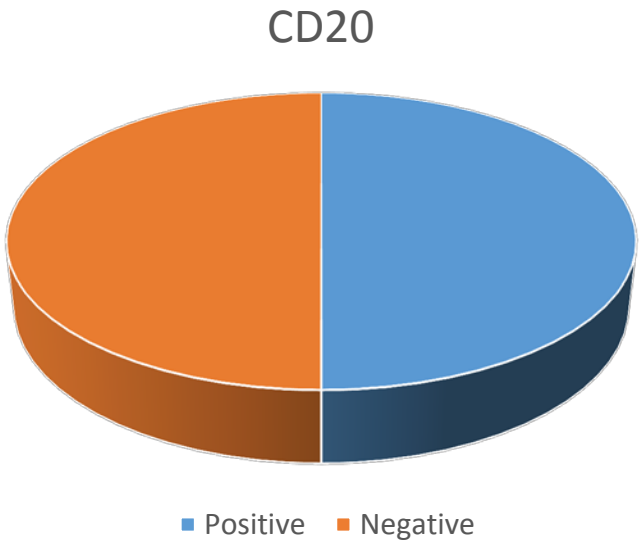
CD19, CD20, CD22



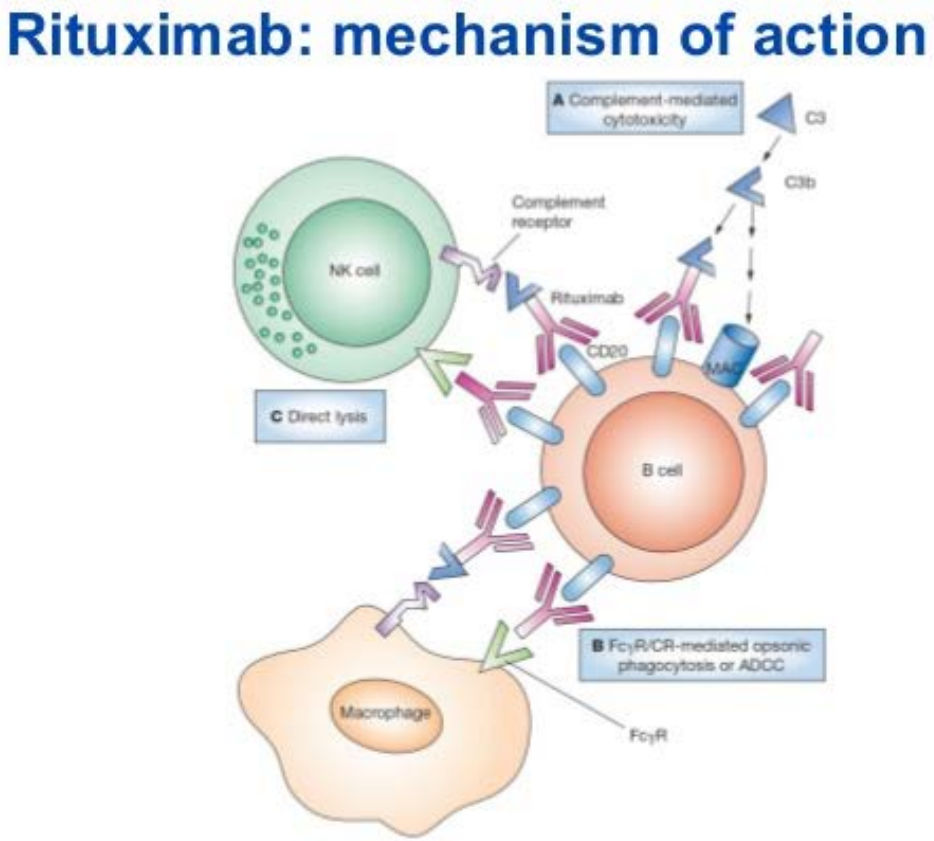
B-ALL has several highly expressed targets for immunotherapy







Rituximab is an anti-CD20 monoclonal antibody

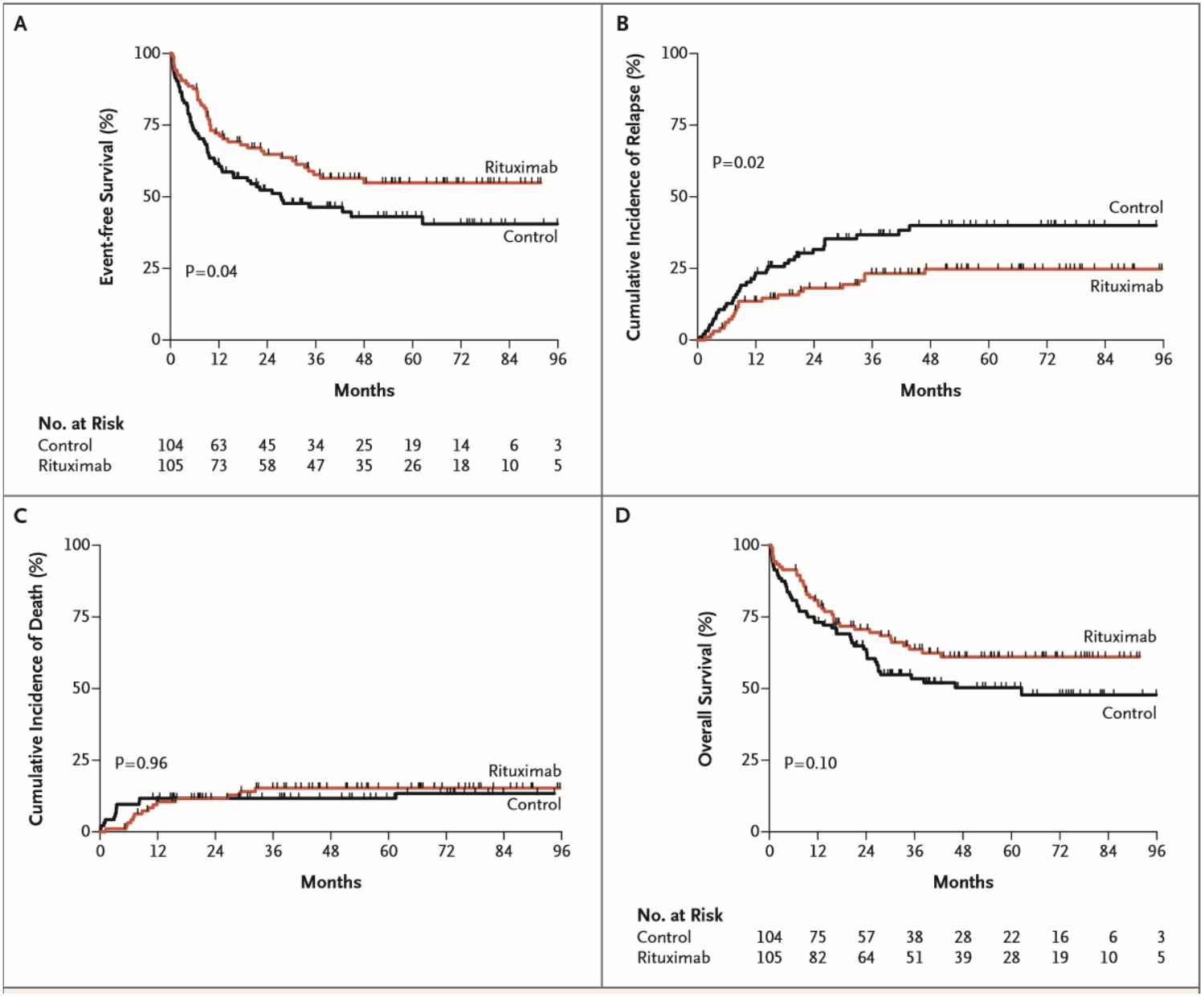


Taylor RP *et al. Nat Clin Pract Rheumatol. 2007;3(2):86-95*

ORIGINAL ARTICLE

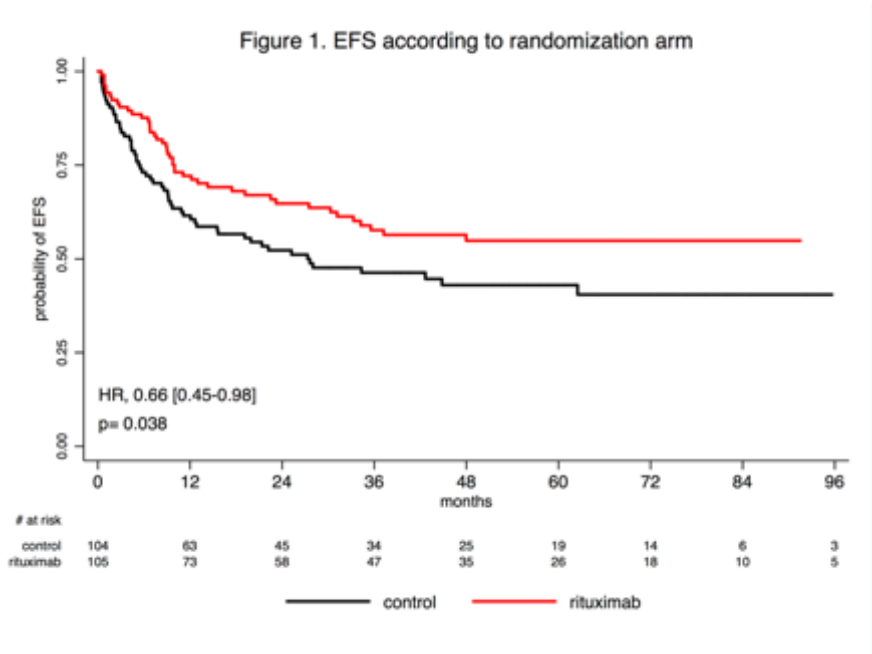
Rituximab in B-Lineage Adult Acute Lymphoblastic Leukemia

Sébastien Maury, M.D., Ph.D., Sylvie Chevret, M.D., Ph.D.,
Xavier Thomas, M.D., Ph.D., Dominik Heim, M.D., Thibaut Leguay, M.D.,
Françoise Huguet, M.D., Patrice Chevallier, M.D., Ph.D.,
Mathilde Hunault, M.D., Ph.D., Nicolas Boissel, M.D., Ph.D.,
Martine Escoffre-Barbe, M.D., Urs Hess, M.D., Norbert Vey, M.D.,
Jean-Michel Pignon, M.D., Thorsten Braun, M.D., Ph.D.,
Jean-Pierre Marolleau, M.D., Ph.D., Jean-Yves Cahn, M.D., Yves Chalandon, M.D.,
Véronique Lhéritier, R.N., M.P.H., Kheira Beldjord, Pharm.D., Ph.D.,
Marie C. Béné, Pharm.D., Ph.D., Norbert Ifrah, M.D.,
and Hervé Dombret, M.D., for GRAALL*

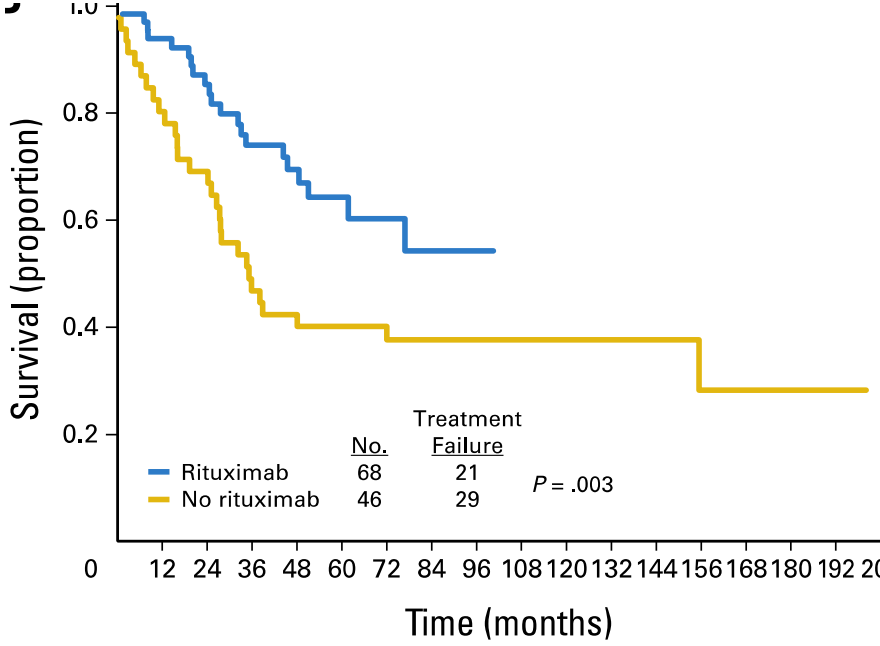

A
Event-free Survival (%)
100
75
50
25
0
Rituximab
Control
P=0.04
0 12 24 36 48 60 72 84 96
Months
No. at Risk
Control 104 63 45 34 25 19 14 6 3
Rituximab 105 73 58 47 35 26 18 10 5
B
Cumulative Incidence of Relapse (%)
P=0.02
Control
Rituximab
Months
C
Cumulative Incidence of Death (%)
P=0.96
Rituximab
Control
Months
D
Overall Survival (%)
Rituximab
Control
P=0.10
Months
No. at Risk
Control 104 75 57 38 28 22 16 6 3
Rituximab 105 82 64 51 39 28 19 10 5

The addition of Rituximab to up-front therapy in CD20+ ALL improves outcome

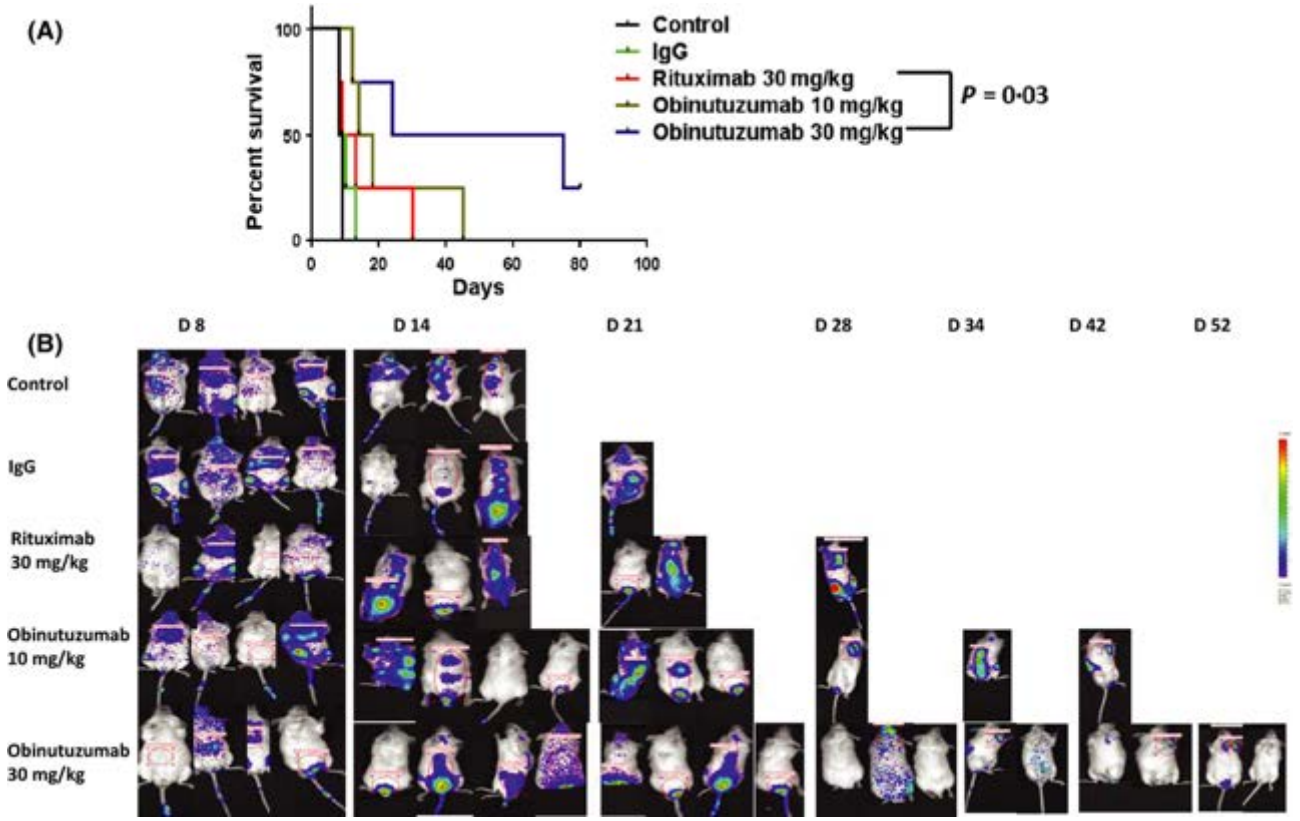
Paediatric-Inspired Regimens – GRAALL05+R



Adult Regimens – R-HyperCVAD (MD Anderson)



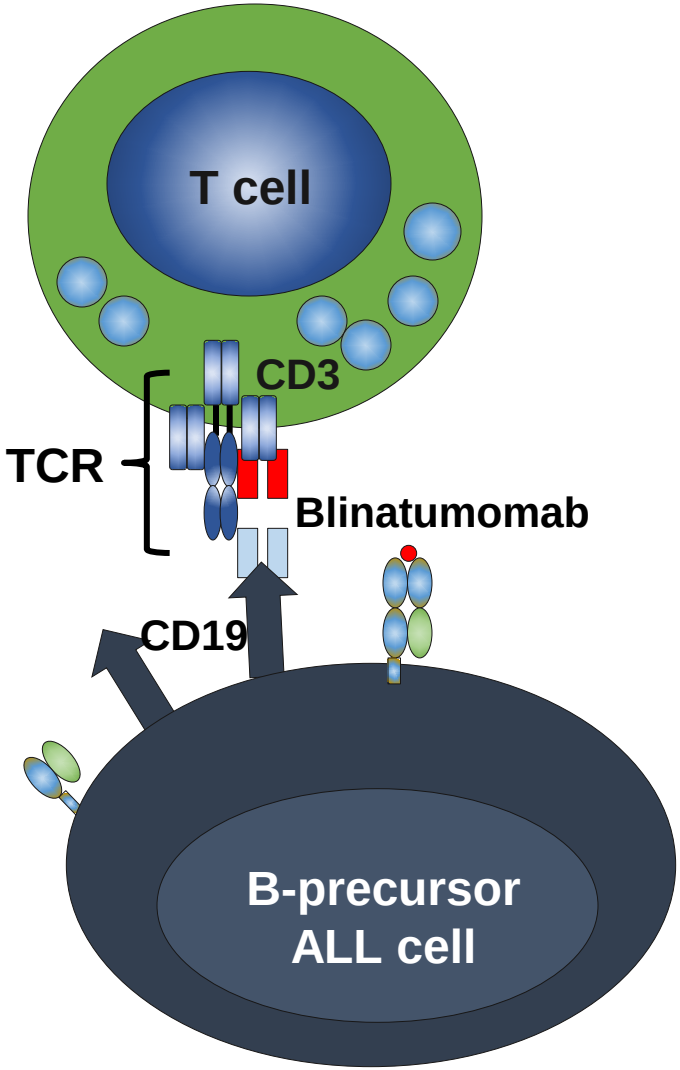
Other anti-CD20 monoclonal antibodies may have a role in ALL



Awasthi et al, BJH, 2015

- Obinutuzumab (GA-101) is a glycoengineered anti-CD20 antibody
- Induces more direct cell death by apoptosis
- Improved response and survival in mouse xenograft model

Blinatumomab



BiTE technology

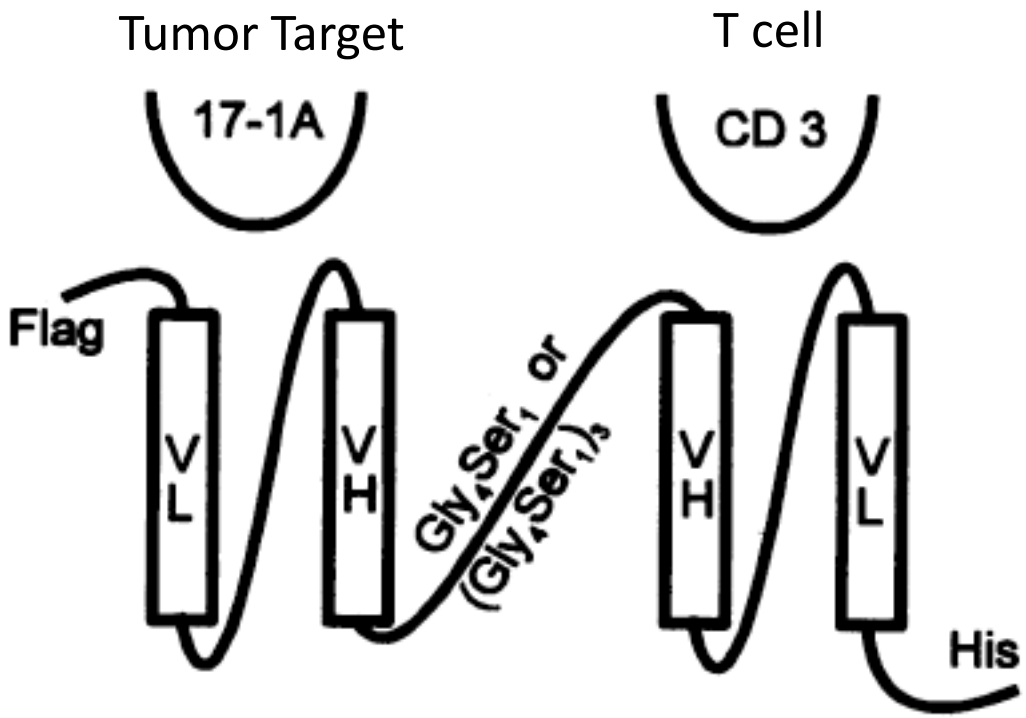
Proc. Natl. Acad. Sci. USA
Vol. 92, pp. 7021–7025, July 1995
Immunology

A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity

MATTHIAS MACK, GERT RIETHMÜLLER, AND PETER KUFER

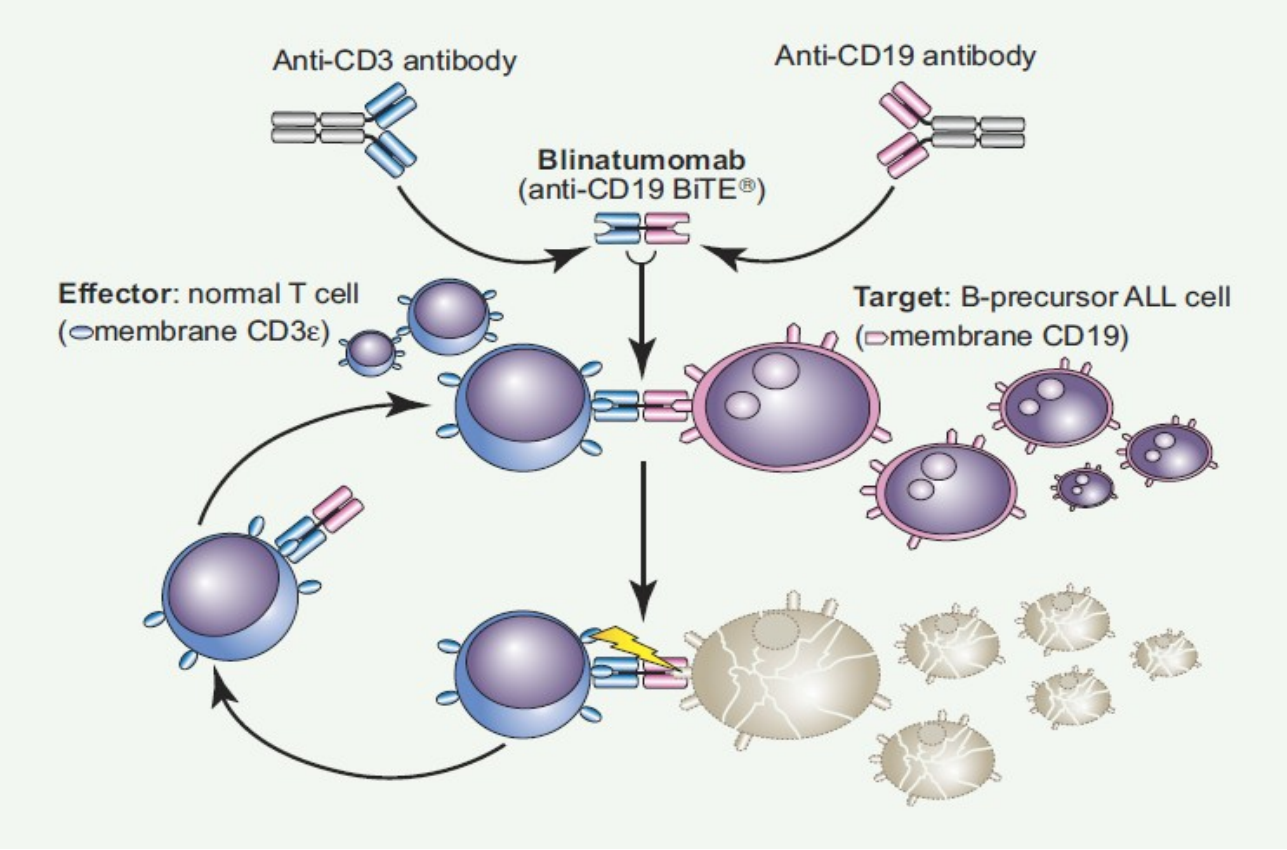
Institut für Immunologie, Goethestrasse 31, D-80336 Munich, Germany

Communicated by Gunter Blobel, The Rockefeller University, New York, NY, April 14, 1995



Immunological Speed-dating

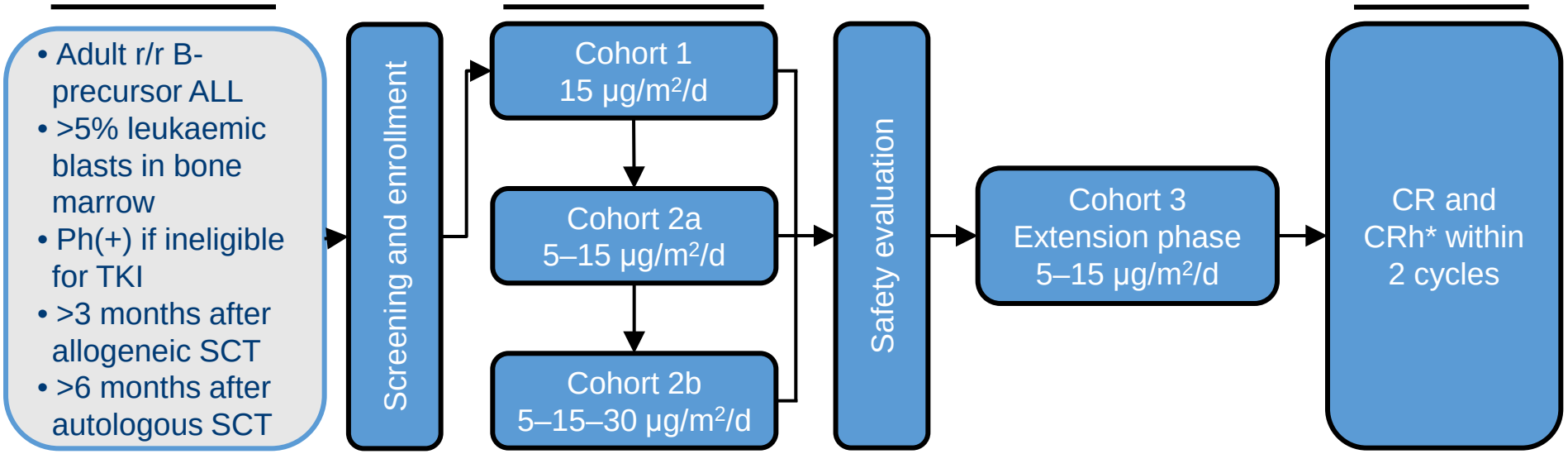
Blinatumomab Mechanism of Action



ALL = acute lymphoblastic leukemia; BiTE = bispecific T-cell engager; CD = cluster of differentiation.

Bassan R. *Blood*. 2012;120:5094-5095.

Open-label, multicentre, exploratory, phase II study (study 206)



Blinatumomab cIV, 4 weeks on/2 weeks off, for up to 5 cycles

Consolidation after CR/CRh* within the first 2 cycles:

- 3 more cycles of blinatumomab *or*
- Allogeneic SCT

CR, complete remission; *CRh, CR with only partial haematological recovery: ≤ 5% blasts in the bone marrow, no evidence of circulating blasts or extra-medullary disease, partial recovery of peripheral blood counts (at least platelets >50,000/µL, Hb >7 g/dL, and ANC >500/µL); Ph, Philadelphia chromosome; SCT, stem cell transplant; TKI, tyrosine kinase inhibitor

Topp MS et al. J Clin Oncol 2014;32:4134–40

Response	Total N=36 n (%)
CR/CRh	25 (69)
CR	15 (42)
CRh	10 (28)
Partial remission*	2 (6)
Hypocellular bone marrow	3 (8)
Refractory	4 (11)
Not evaluable†	2 (6)

- Of those achieving CR/CRh
  - 13/25 (52%) went on to receive an allogeneic SCT
  - 22/25 (88%) achieved molecular remission (MRD-) across all cycles

Blinatumomab in Relapsed/Refractory ALL: Efficacy

Outcome	All Pts (N = 189)
CR or CRh in first 2 cycles, %	43
CR in first 2 cycles, %	33
MRD negativity in first 2 cycles, %*	82
Median OS, mos ▪ All pts ▪ MRD-negative CR ▪ MRD-positive CR	 6.1 11.5 6.7
Median RFS, mos ▪ CR + CRh ▪ CR ▪ CRh	 5.9 6.9 5.0
Allogeneic HCT, %* ▪ After CR ▪ After CRh	40 44 22
100-day mortality after allogeneic HCT, %	11

*Of pts in CR or CRh.

Topp MS, et al. Lancet Oncol. 2015;16:57-66.

Blinatumomab Improved Overall Survival in Patients With Relapsed or Refractory Philadelphia-Negative B-cell Precursor Acute Lymphoblastic Leukemia in a Randomized, Open-Label Phase 3 Study (TOWER)

Topp MS, et al. Slides presented at: 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

ORIGINAL ARTICLE

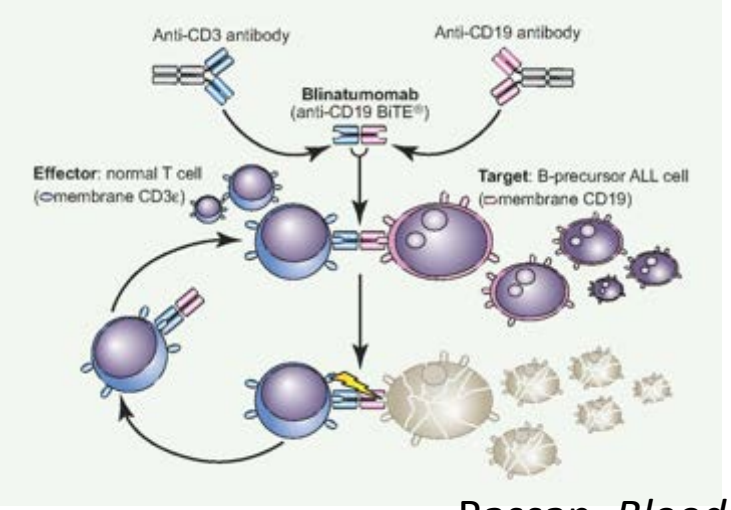
Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Hagop Kantarjian, M.D., Anthony Stein, M.D., Nicola Gökbuget, M.D., Adele K. Fielding, M.B., B.S., Ph.D., Andre C. Schuh, M.D., Josep-Maria Ribera, M.D., Ph.D., Andrew Wei, M.B., B.S., Ph.D., Hervé Dombret, M.D., Robin Foà, M.D., Renato Bassan, M.D., Önder Arslan, M.D., Miguel A. Sanz, M.D., Ph.D., Julie Bergeron, M.D., Fatih Demirkan, M.D., Ewa Lech-Maranda, M.D., Ph.D., Alessandro Rambaldi, M.D., Xavier Thomas, M.D., Ph.D., Heinz-August Horst, M.D., Ph.D., Monika Brüggemann, M.D., Wolfram Klapper, M.D., Ph.D., Brent L. Wood, M.D., Ph.D., Alex Fleishman, M.S., Dirk Nagorsen, M.D., Ph.D., Christopher Holland, M.S., Zachary Zimmerman, M.D., Ph.D., and Max S. Topp, M.D.

N Engl J Med 2017; 376:836-847 | March 2, 2017 | DOI: 10.1056/NEJMoa1609783

TOWER Phase III Study of Blinatumomab in R/R ALL

- Randomised phase III study of the BiTE® (Bi-specific T-cell Engager) Blinatumomab vs SOC chemotherapy in Relapsed/Refractory B-precursor Acute Lymphoblastic Leukaemia
- Primary objective to evaluate overall survival vs SOC chemotherapy
- Previously demonstrated efficacy in phase II studies in R/R B-ALL and in MRD+ B-ALL

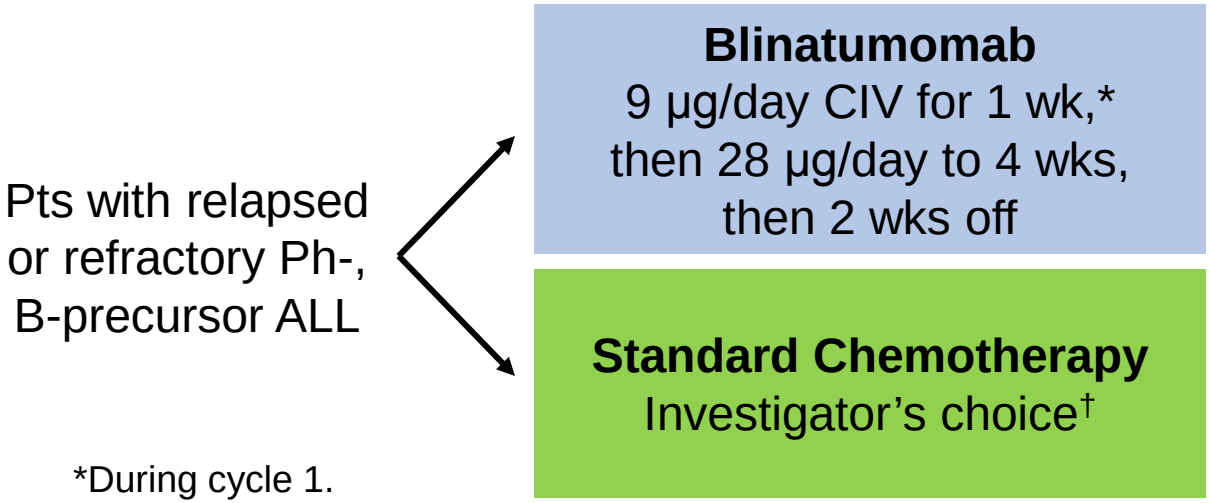


Bassan, *Blood* 2012

Topp et al, EHA 2016

TOWER: Phase III Trial of Blinatumomab for Relapsed/Refractory ALL

- Multicenter, randomized, open-label phase III study
- Primary endpoint: OS

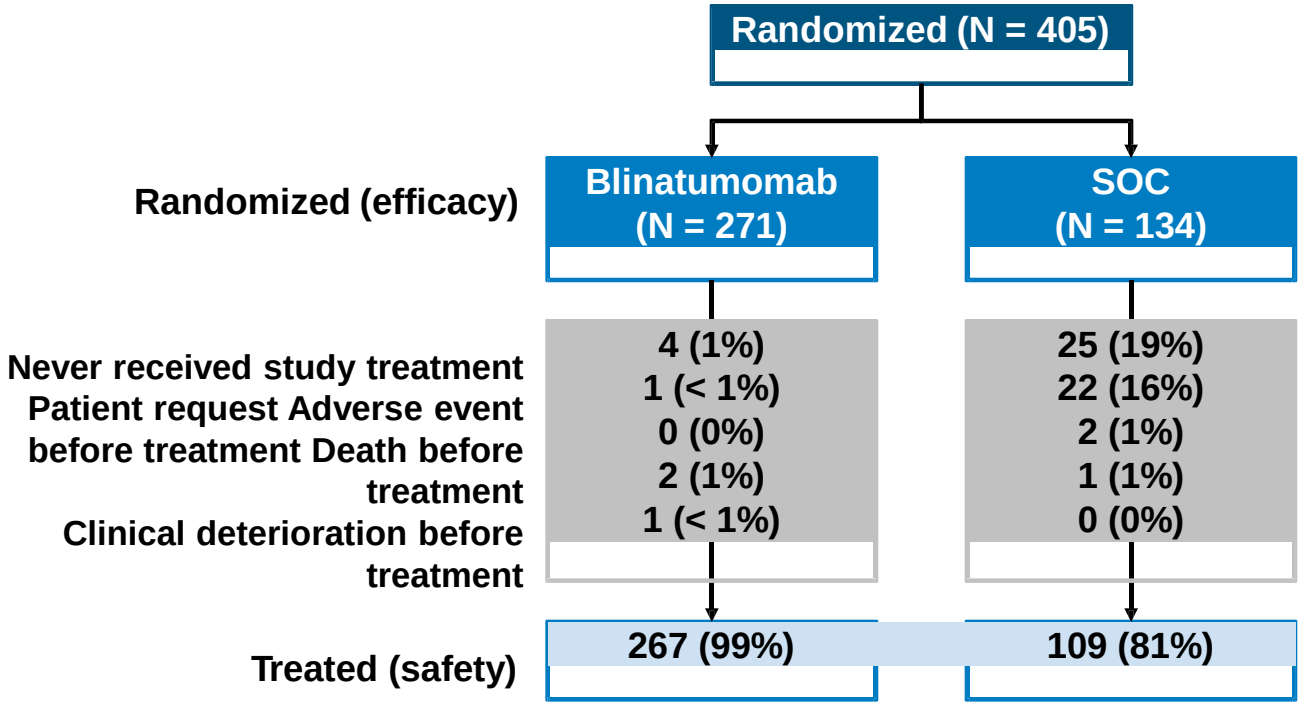


*During cycle 1.

†Options include:
- FLAG ± anthracycline-based regimen
- HiDAC-based regimen ± anthracycline
- High-dose methotrexate–based regimen
- Clofarabine- or clofarabine-based regimens

ClinicalTrials.gov. NCT02013167.

Analysis Sets

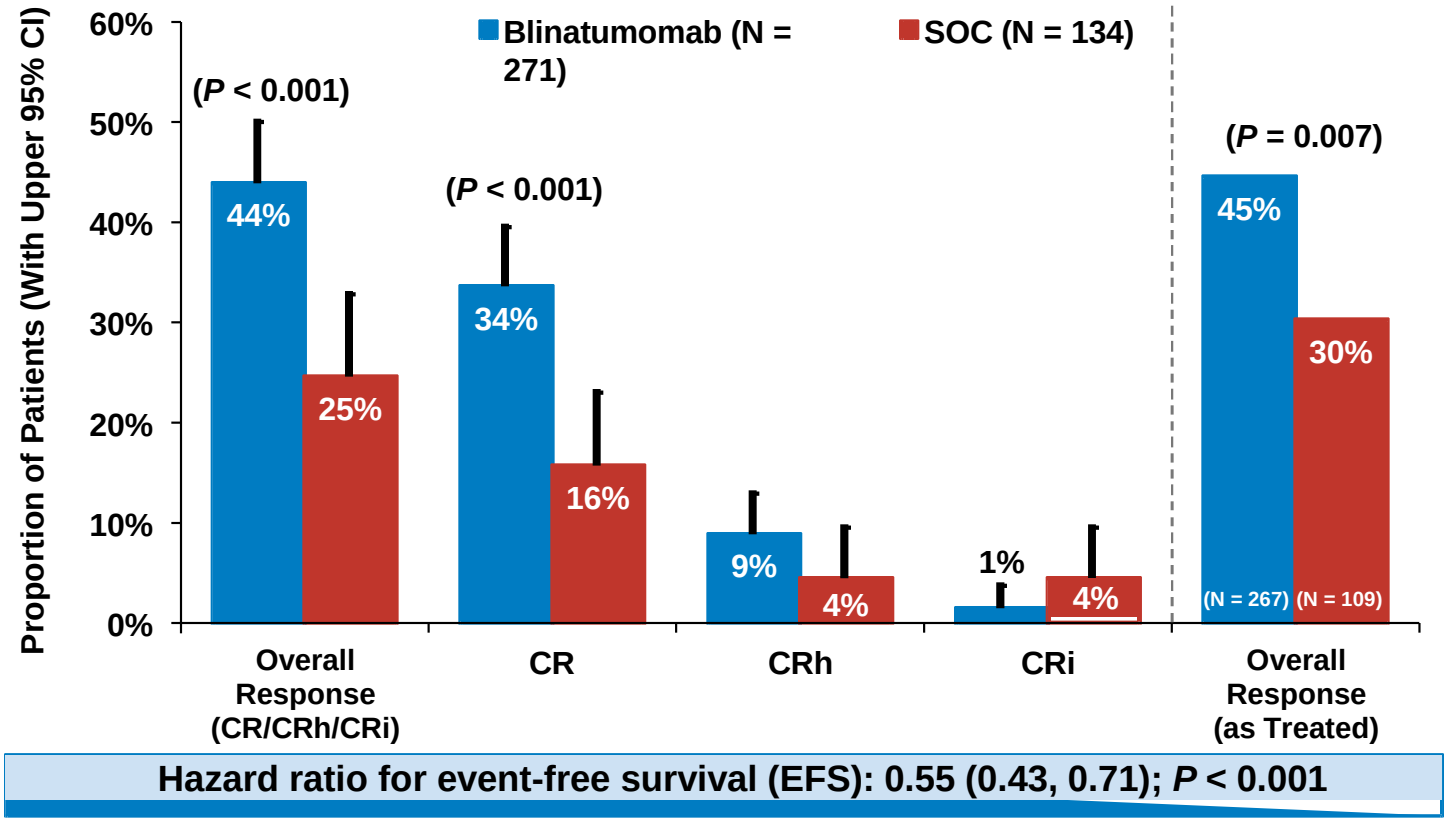


SOC, n (%): 49 (45%) FLAG ± anthracycline; 19 (17%) HiDAC-based; 22 (20%) high-dose methotrexate-based; and 19 (17%) clofarabine-based

HiDAC = high-dose cytarabine; SOC = standard of care; FLAG = Fludarabine, Arabinofuranosyl cytidine, Granulocyte colony-stimulating factor

Topp MS, et al. Slides presented at: 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

Hematologic Response in Induction

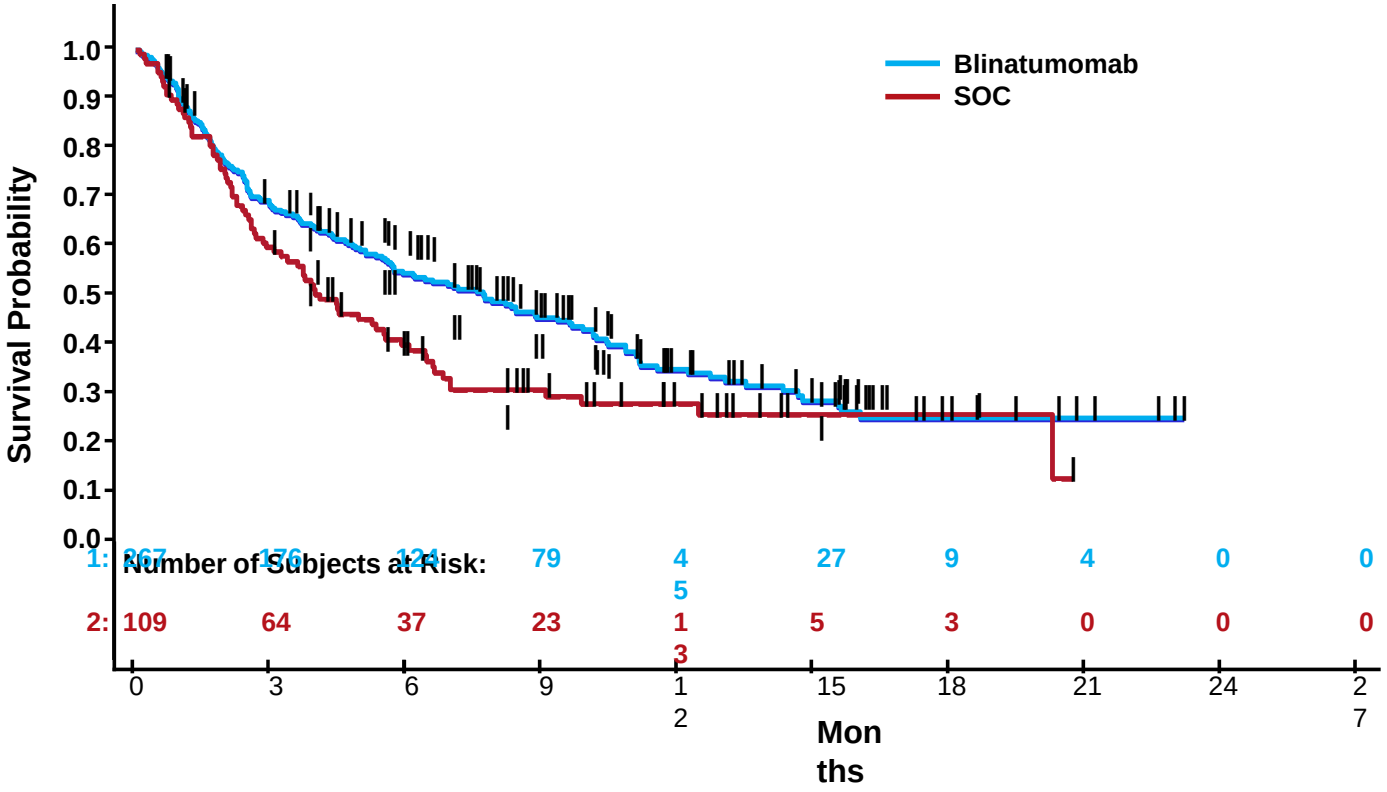


CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete hematologic recovery; SOC = standard of care.

Topp MS, et al. Slides presented at: 21st Congress of the European Hematology Association; June 9-12, 2016;

Copenhagen, Denmark.

Overall Survival (as Treated)



SOC = standard of care.

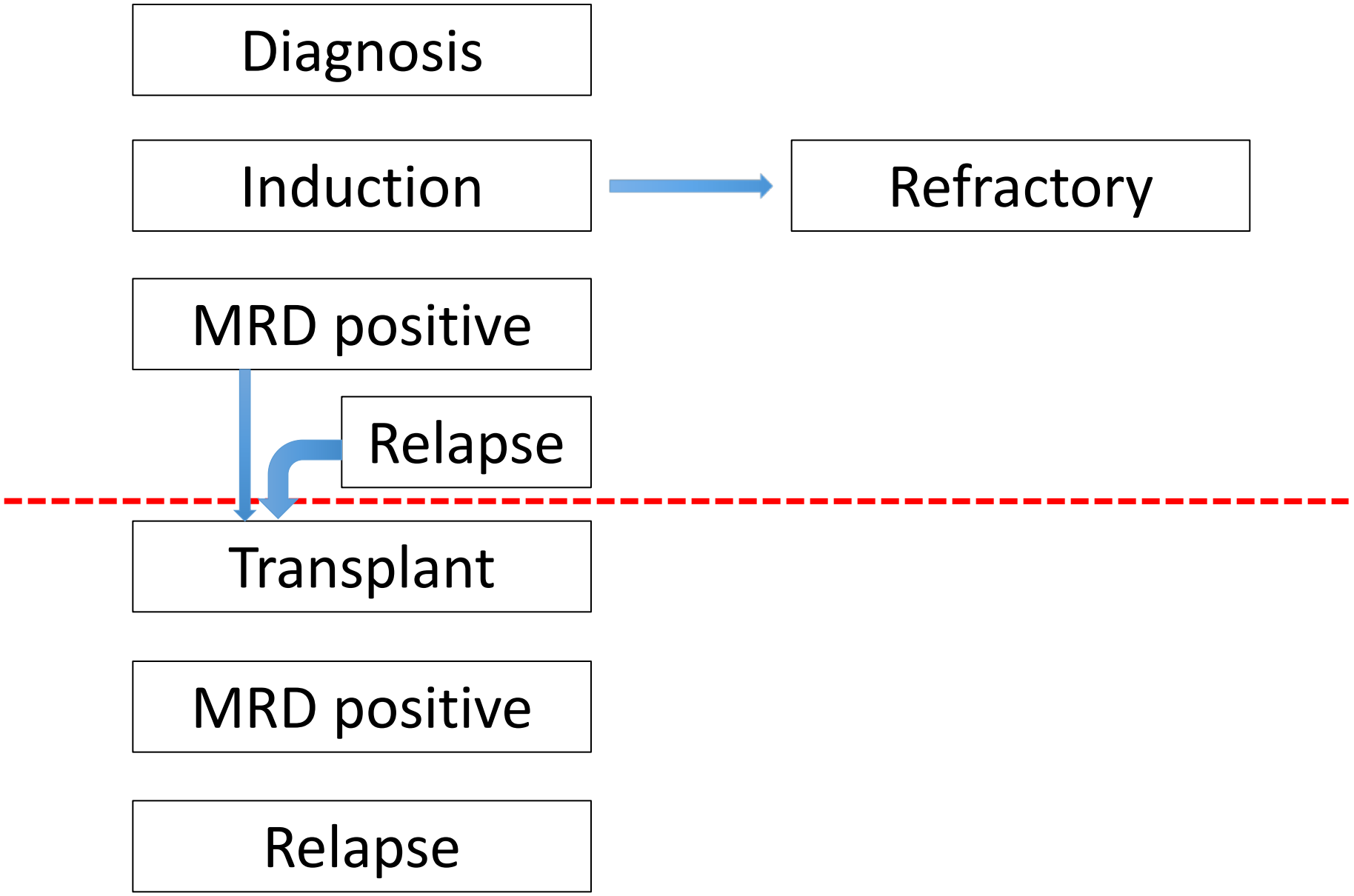
Topp MS, et al. Slides presented at: 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

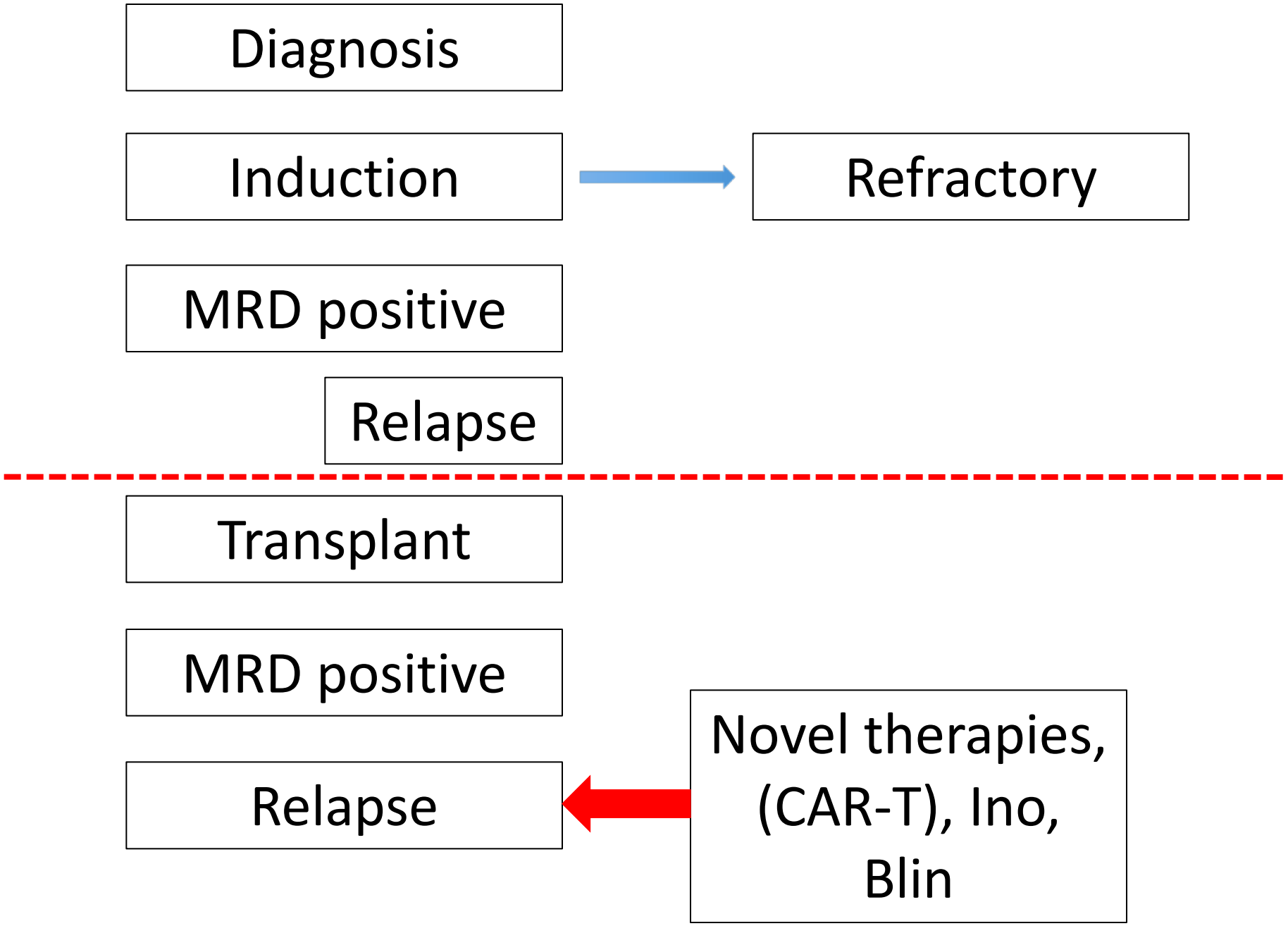
Conclusions

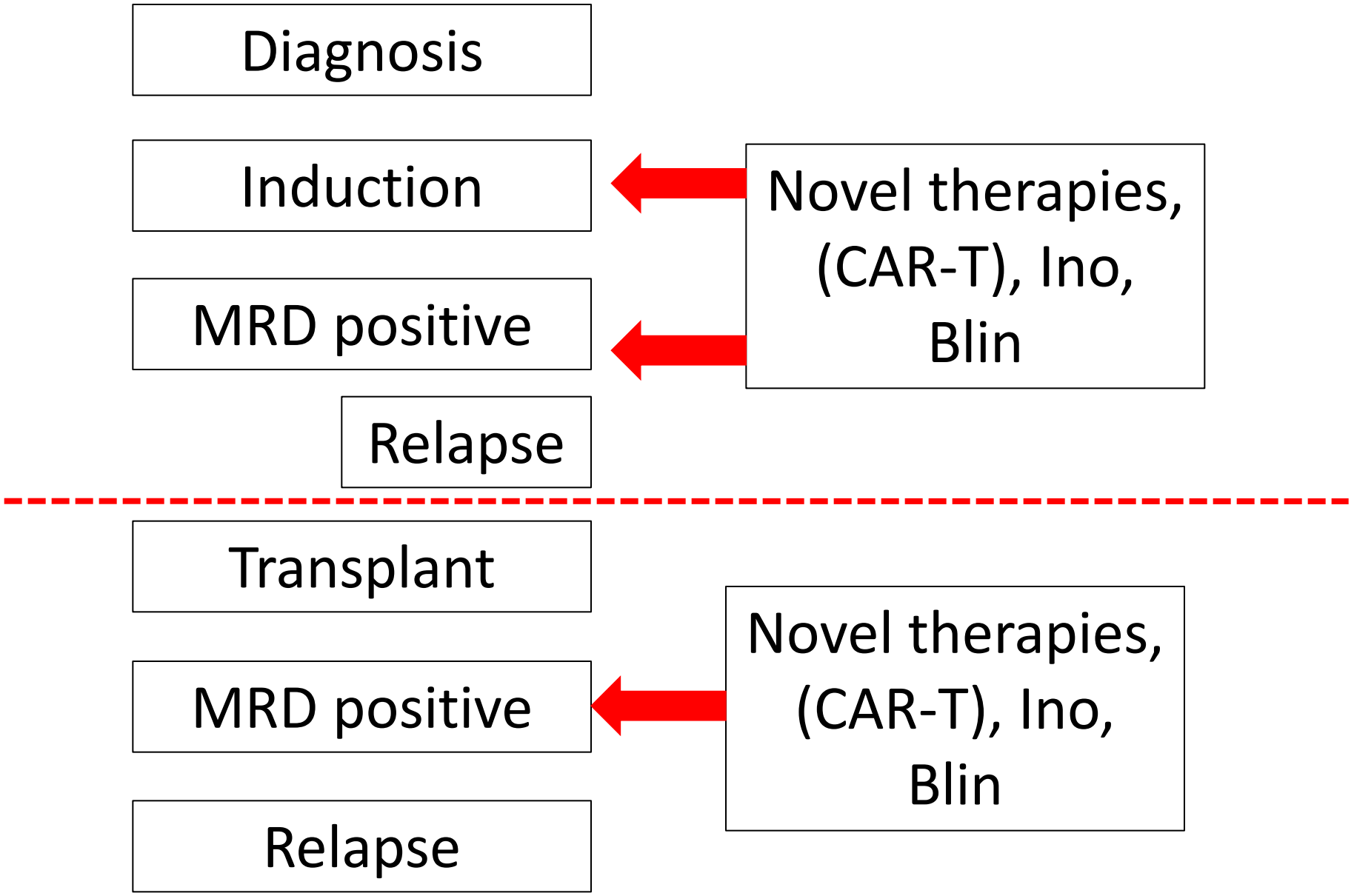
- **In this primary analysis of the phase 3 TOWER study of adults with Ph– r/r pre-B ALL, blinatumomab prolonged overall survival vs SOC**
  - **This was the first study to show improved survival with immunotherapy vs SOC in R/R ALL**
  - **Survival favored blinatumomab in each subgroup**
  - **Similar difference in survival after censoring for alloHSCT**
- **Secondary efficacy endpoints (hematologic and molecular remission; EFS) also favored blinatumomab vs SOC**
- **Adverse events in the blinatumomab group were consistent with previous studies**
- **Grade ≥ 3 neutropenia and infection appeared less frequently with blinatumomab, while neurologic events appeared at a similar rate**

ALL = acute lymphoblastic leukemia; alloHSCT = allogeneic hematopoietic stem cell transplantation; EFS = event-free survival; Ph– = Philadelphia-negative; r/r = relapsed/refractory; SOC = standard of care.

Topp MS, et al. Slides presented at: 21st Congress of the European Hematology Association; June 9-12, 2016; Copenhagen, Denmark.

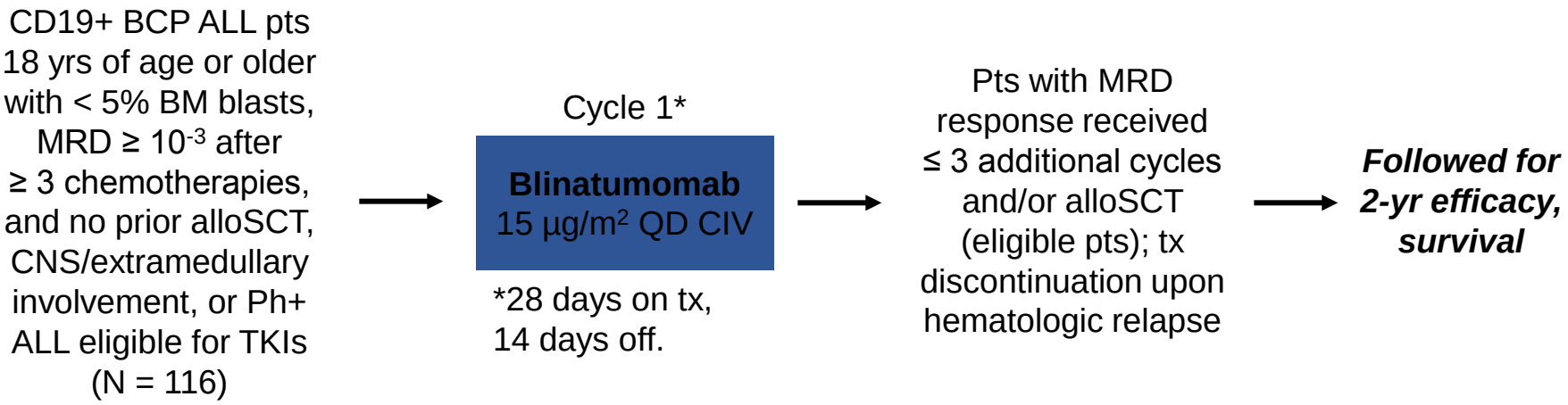

Diagnosis
Induction
Refractory
MRD positive
Relapse
Transplant
MRD positive
Relapse


Diagnosis
Induction
Refractory
MRD positive
Relapse
Transplant
MRD positive
Relapse
Novel therapies, (CAR-T), Ino, Blin


Diagnosis
Induction
MRD positive
Relapse
Novel therapies, (CAR-T), Ino, Blin
Transplant
MRD positive
Relapse
Novel therapies, (CAR-T), Ino, Blin

Blinatumomab in MRD-Positive B-Cell Precursor ALL

- International, multicenter, open-label phase II study from 2010-2013
- Primary endpoint: achieving MRD < 10^{-4} in cycle 1



Gökbuget N, et al. ASH 2015. Abstract 680.

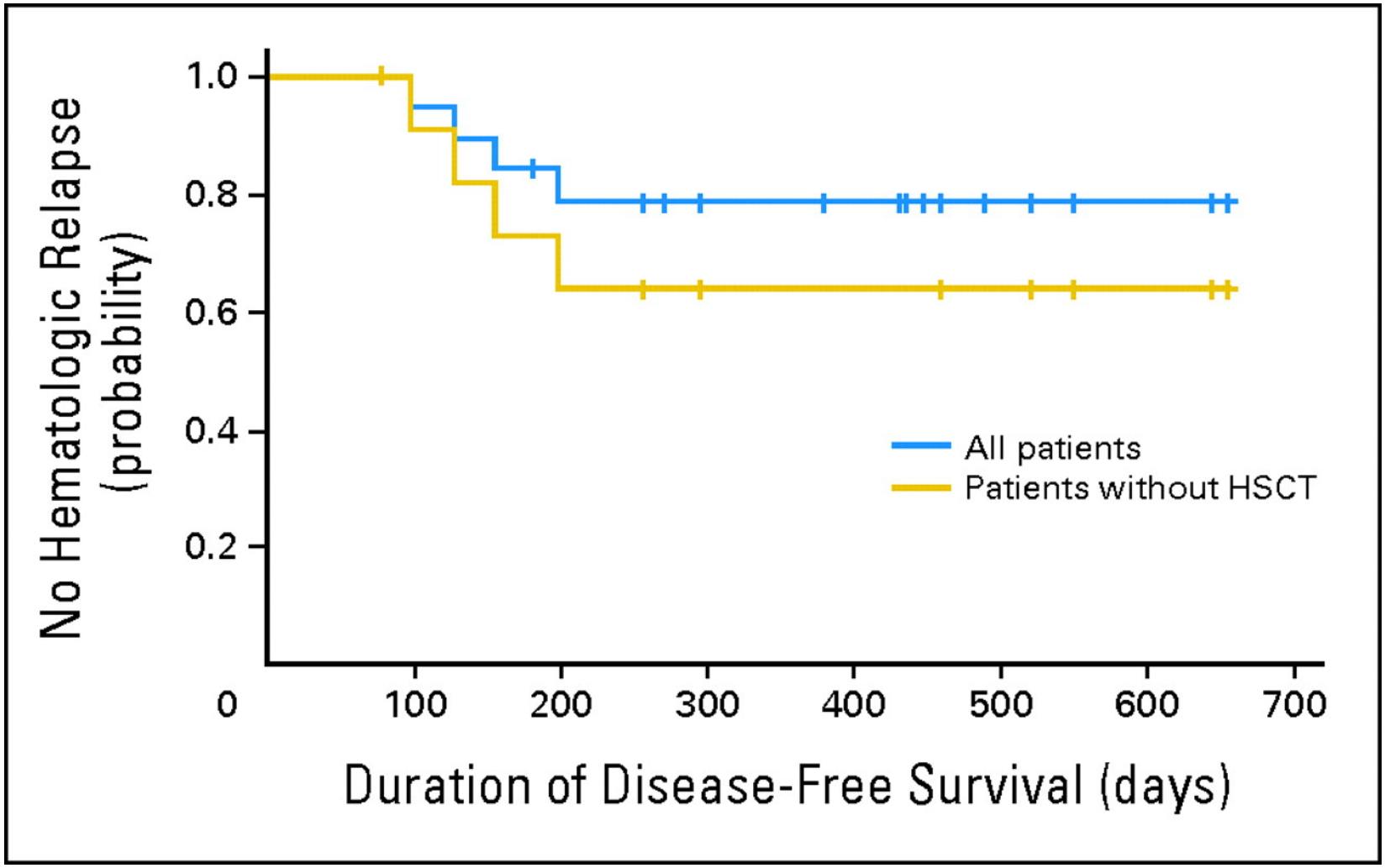
Blinatumomab in MRD-Positive B-Cell Precursor ALL: Efficacy

Outcome, Mos	Blinatumomab (n = 110)	MRD Complete vs Incomplete, P Value
Median OS ▪ MRD complete responder ▪ MRD incomplete responder	36.5 38.9 12.5	.002
Median RFS ▪ CR1 ▪ CR2/CR3 ▪ MRD complete responder ▪ MRD incomplete responder	18.9 24.6 11.0 23.6 5.7	.003
Median duration of remission ▪ MRD complete responder ▪ MRD incomplete responder	NR NR 17.2	.049

- Median follow-up: 30 mos
- Complete MRD response: 80%
- Transplant realization rate: 72%

Gökbuget N, et al. ASH 2015. Abstract 680.

Time to clinical relapse.

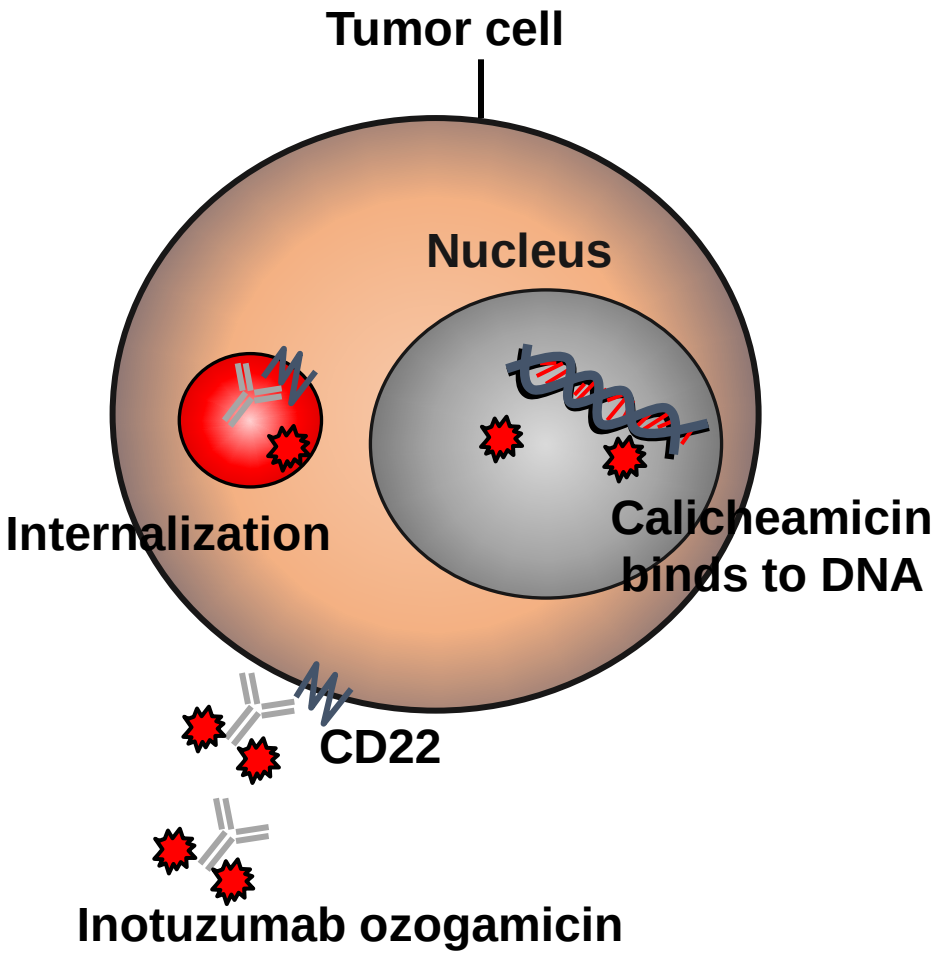


Topp M S et al. JCO 2011;29:2493-2498

JOURNAL OF CLINICAL ONCOLOGY

Inotuzumab Ozogamicin

- Antibody-chemotherapy complex that is rapidly internalized into tumor cells upon binding to CD22 on cell surface
- Cytotoxin calicheamicin is released from the complex inside the tumor cell
  - More potent than other cytotoxic chemotherapeutic agents
- Calicheamicin binds to DNA, inducing double-stranded DNA breaks
- DNA break development followed by apoptosis of the tumor cell



Jabbour E, et al. ASH 2014. Abstract 794.

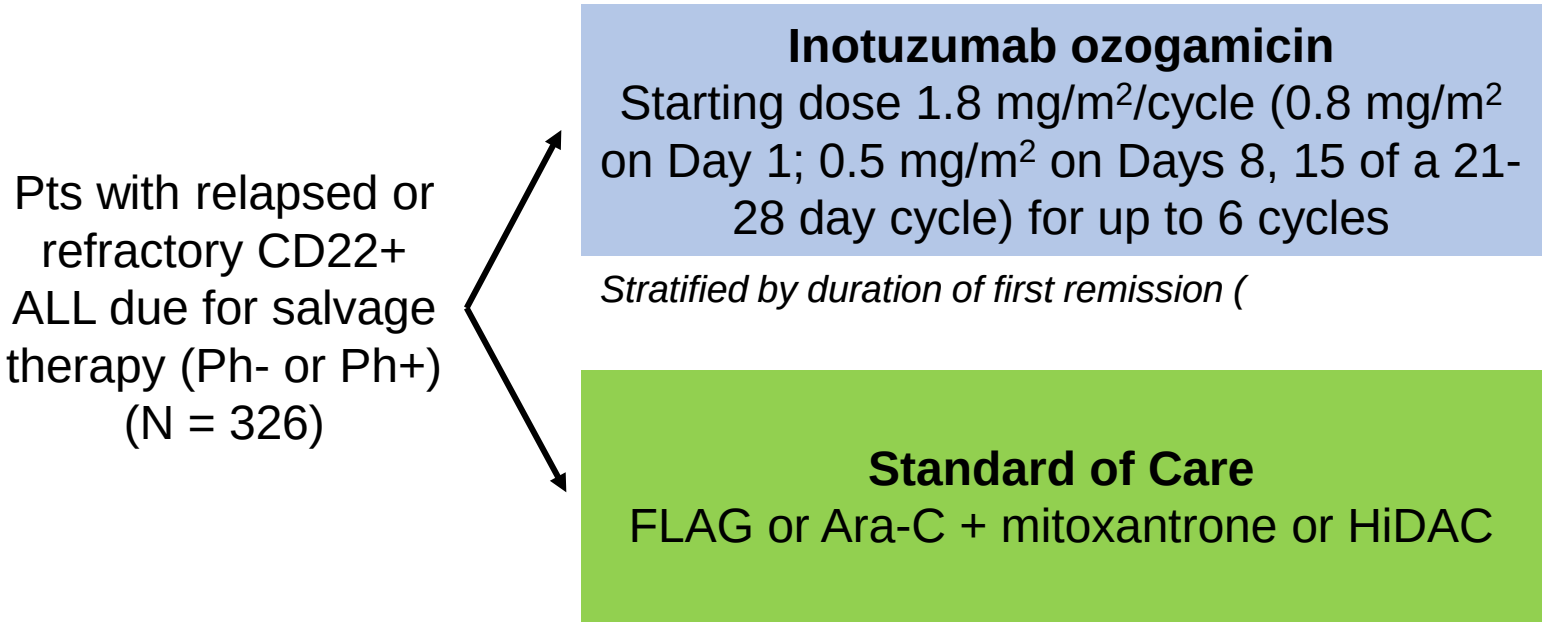
Inotuzumab Ozogamicin for Relapsed/ Refractory Pre–B-Cell ALL

Study	N	Dose	CR/CRi, %	MRD Neg With CR/CRi, %	Median Time to MRD Neg, Days (Range)
Phase II MDACC trial[1]	49	1.8 mg/m^2 Q3-4W	57		
Phase II MDACC trial[2]	41	Weekly 1.8 mg/m^2 (0.8 mg/m^2 on Day 1, 0.5 mg/m^2 on Days 8, 15) Q3-4W	59		
Phase I/II multicenter study	37 (phase I)[3]	Weekly 1.2-1.8 mg/m^2 (total)	68	88	34 (22-141)
	35 (phase II)[4]	Weekly 1.8 mg/m^2 (0.8 mg/m^2 on Day 1, 0.5 mg/m^2 on Days 8, 15) per cycle then 1.6 mg/m^2/cycle upon CR or CRi	66	78	26 (21-80)

1. Kantarjian H, et al. Lancet Oncol. 2012;13:403-411.
2. Kantarjian H, et al. Cancer. 2013;119:2728-2736.
3. DeAngelo DJ, et al. ASH 2013. Abstract 3906.
4. Advani AS, et al. ASH 2014. Abstract 2255.

Phase III Trial of Inotuzumab Ozogamicin in Relapsed/Refractory CD22+ ALL

- Multicenter, randomized, open-label phase III study
- Primary endpoints: CR and OS



ClinicalTrials.gov. NCT01564784.

ORIGINAL ARTICLE

Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia

Hagop M. Kantarjian, M.D., Daniel J. DeAngelo, M.D., Ph.D., Matthias Stelljes, M.D., Giovanni Martinelli, M.D., Michaela Liedtke, M.D., Wendy Stock, M.D., Nicola Gökbuget, M.D., Susan O'Brien, M.D., Kongming Wang, Ph.D., Tao Wang, Ph.D., M. Luisa Paccagnella, Ph.D., Barbara Sleight, M.D., Erik Vandendries, M.D., Ph.D., and Anjali S. Advani, M.D.

Inotuzumab Ozogamicin vs Standard Therapy for Acute Lymphoblastic Leukaemia

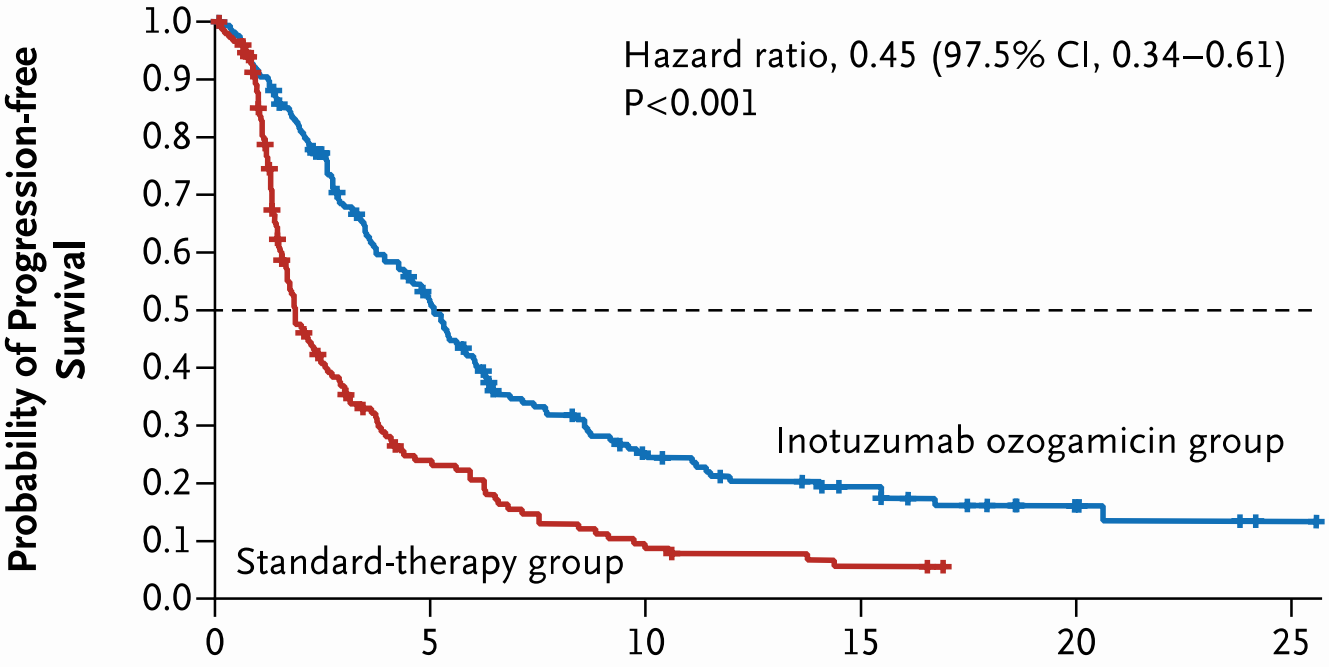
- CR rate of 80.7% vs 29.4%
  - MRD negative in 78.4% of remissions with Ino
- CR's more likely to be MRD negative than CRi
  - 89.7% vs 69.4%

Table 2. Trial End Points in the Remission-Analysis Population.*

End Point	Inotuzumab Ozogamicin Group		Standard-Therapy Group		Between-Group Difference (97.5% CI)	P Value†
	no./total no.	*% (95% CI)*	*no./total no.*	*% (95% CI)*	*percentage points*	
Complete remission or complete remission with incomplete hematologic recovery						
Total	88/109	80.7 (72.1–87.7)	32/109	29.4 (21.0–38.8)	51.4 (38.4–64.3)	<0.001
Bone marrow blast results below threshold for minimal residual disease	69/88	78.4 (68.4–86.5)	9/32	28.1 (13.7–46.7)	50.3 (29.9–70.6)	<0.001
Complete remission						
Total	39/109	35.8 (26.8–45.5)	19/109	17.4 (10.8–25.9)	18.3 (5.2–31.5)	0.002
Bone marrow blast results below threshold for minimal residual disease	35/39	89.7 (75.8–97.1)	6/19	31.6 (12.6–56.6)	58.2 (31.9–84.4)	<0.001
Complete remission with incomplete hematologic recovery						
Total	49/109	45.0 (35.4–54.8)	13/109	11.9 (6.5–19.5)	33.0 (20.3–45.8)	<0.001
Bone marrow blast results below threshold for minimal residual disease	34/49	69.4 (54.6–81.7)	3/13	23.1 (5.0–53.8)	46.3 (16.2–76.4)	0.004

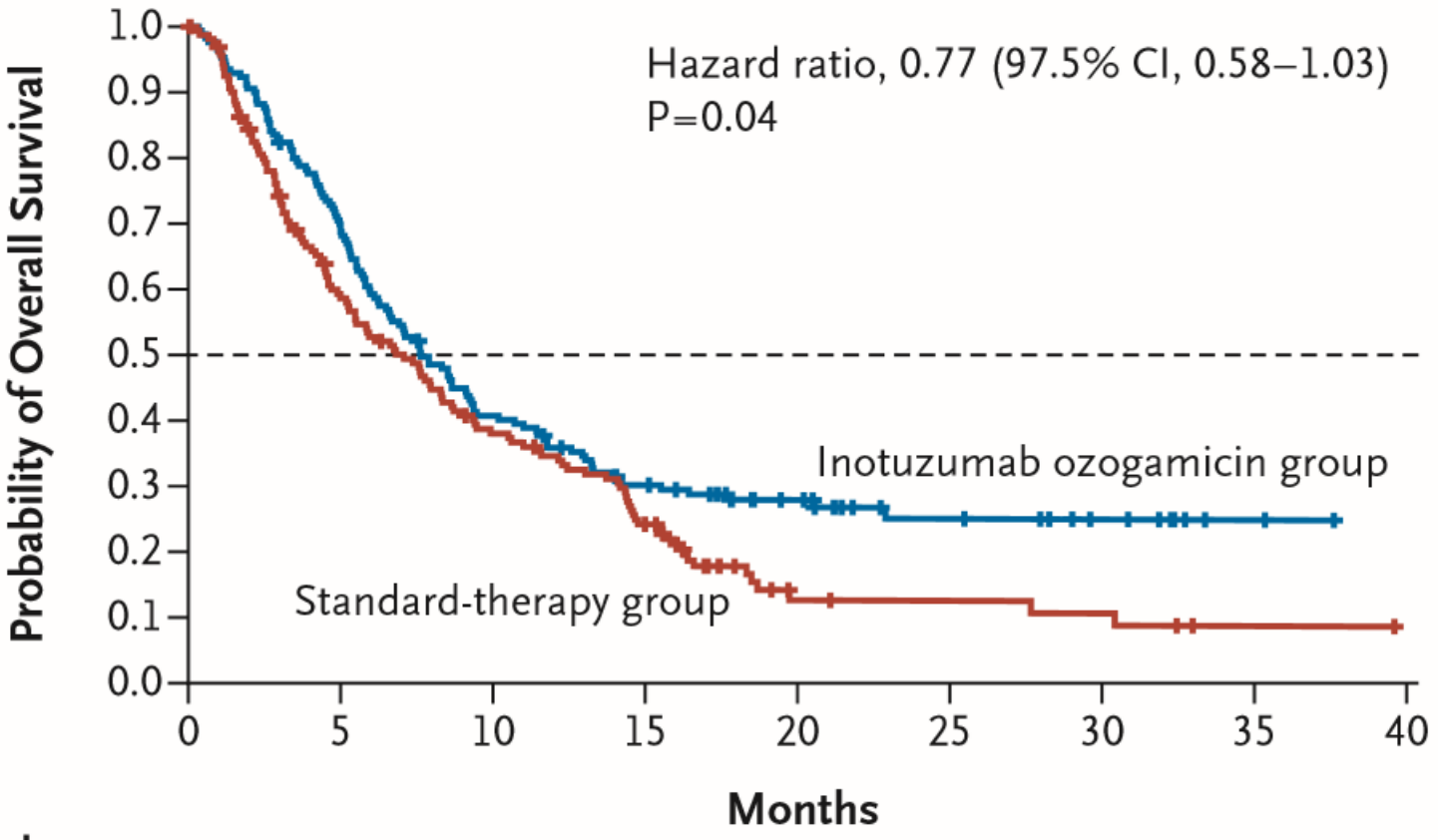
Kantarjian et al, EHA 2016 + NEJM 2016

The results of the phase III INO-VATE study demonstrate improvement in survival over salvage chemotherapy in R/R ALL



No. at Risk						
Inotuzumab ozogamicin group	164	72	28	16	6	1
Standard-therapy group	162	24	6	2	0	0

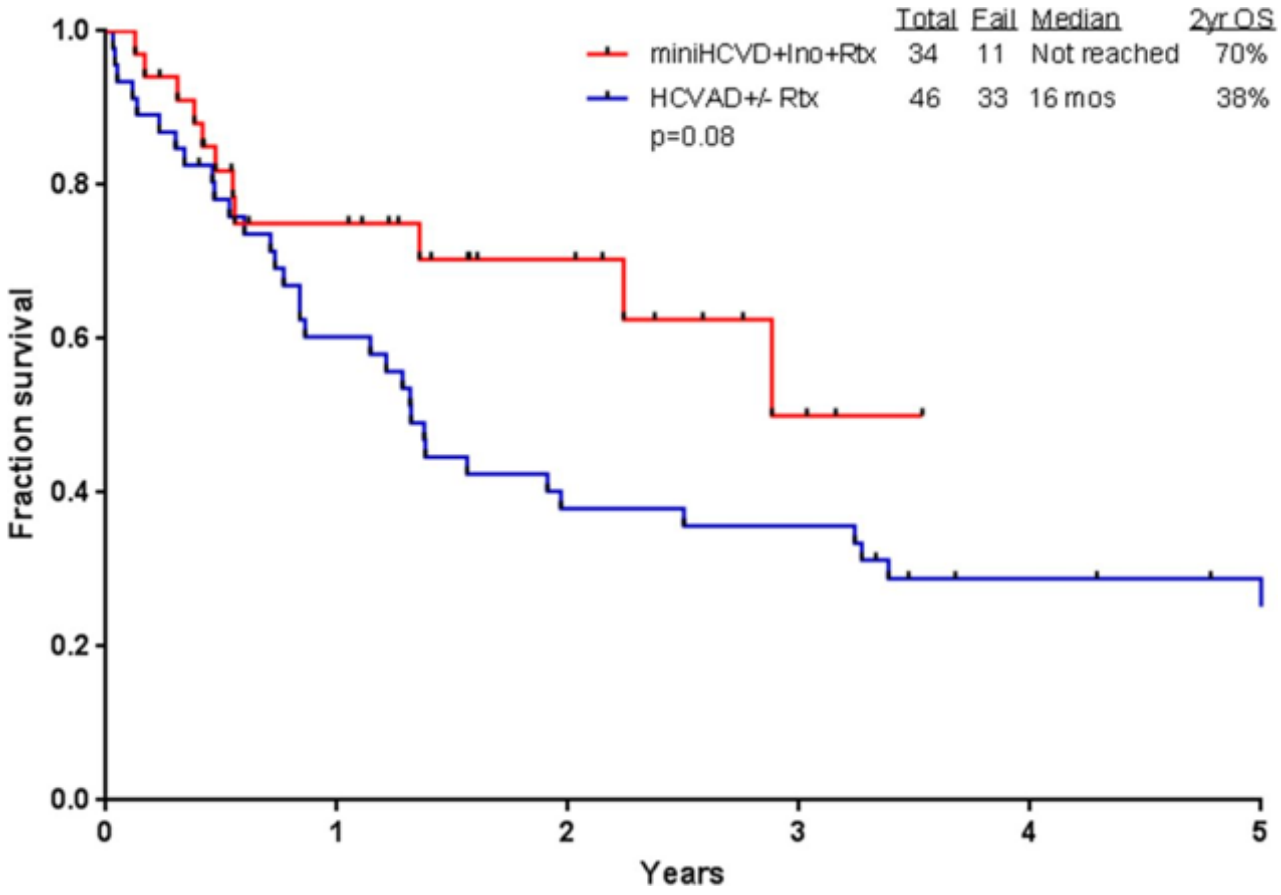
C Overall Survival



No. at Risk

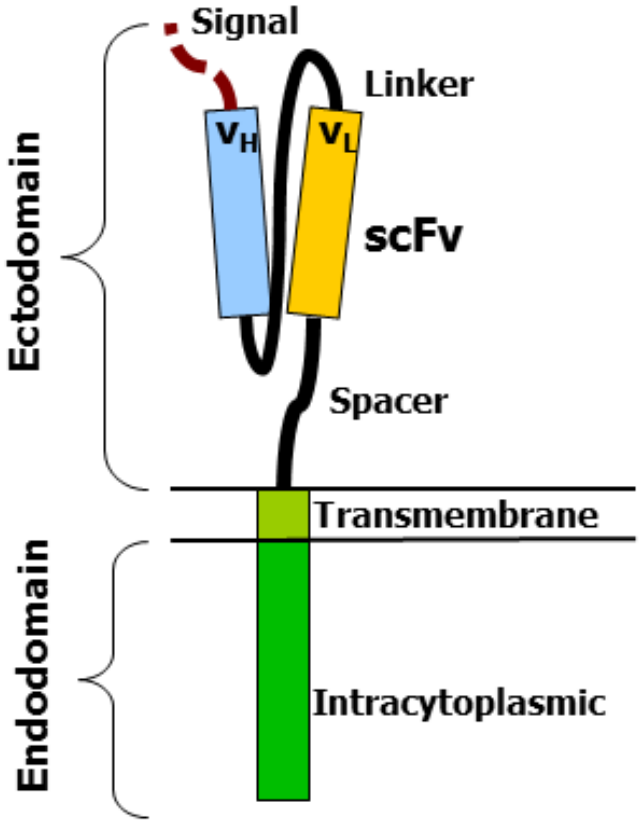
Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0
Standard-therapy group	162	85	51	30	6	5	4	1	0

Up-front use of targeted therapies



Jabbour et al, ASH 2015

Chimeric Antigen Receptor T-cells
CART



- CART cells are modified T-cells
- Engineered to express an immunoglobin receptor to target antigen linked with a spacer to an intracytolasmic domain which leads to T-cell activation
- Able to be targeted at specific antigen targets
- Currently CD19, CD22 and CD123 CART cells are under active investigation

Image: https://en.m.wikipedia.org/wiki/Chimeric_antigen_receptor#/media/File%3ACAR_cartoon.png

Generation of CARTs

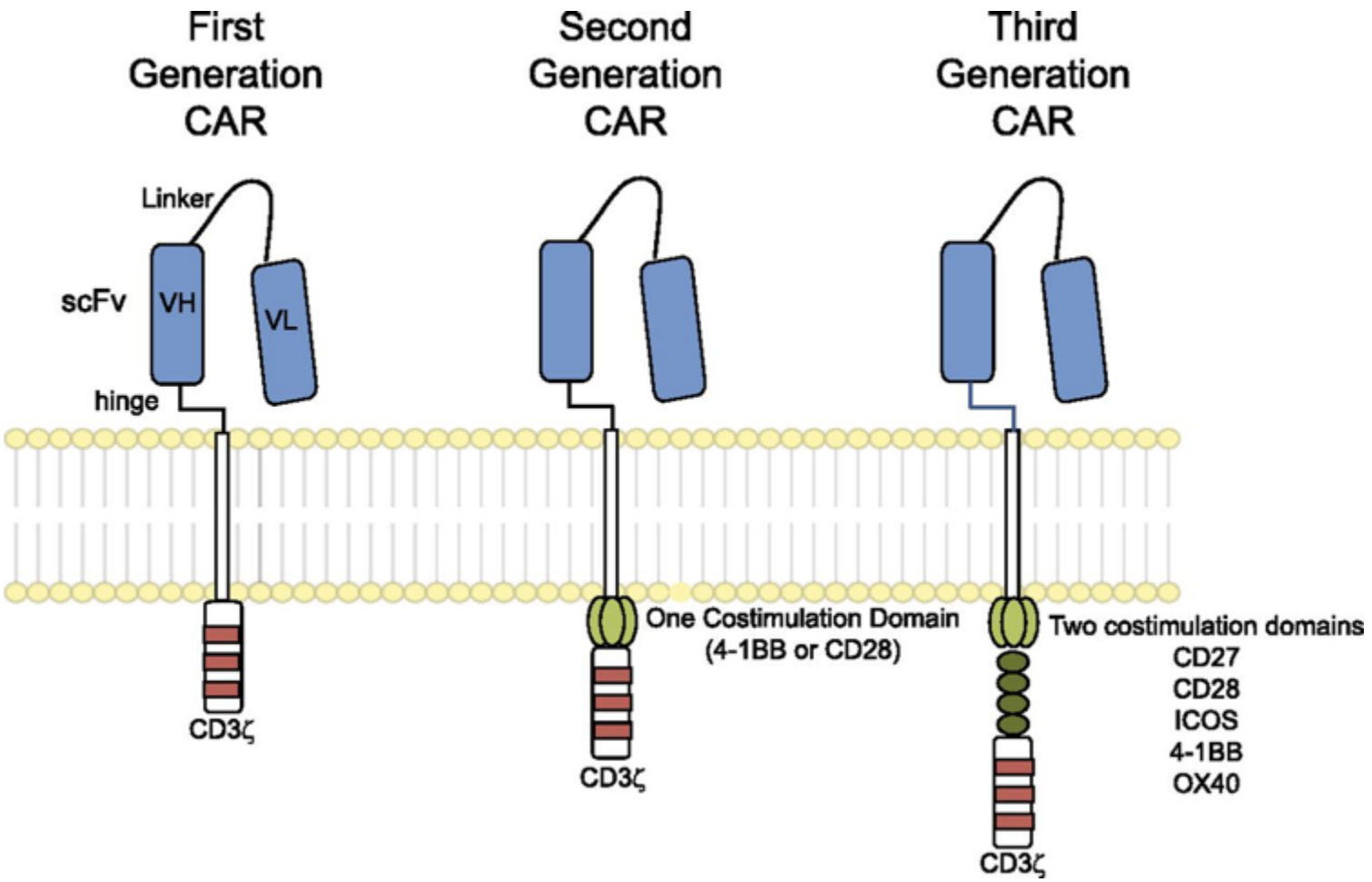
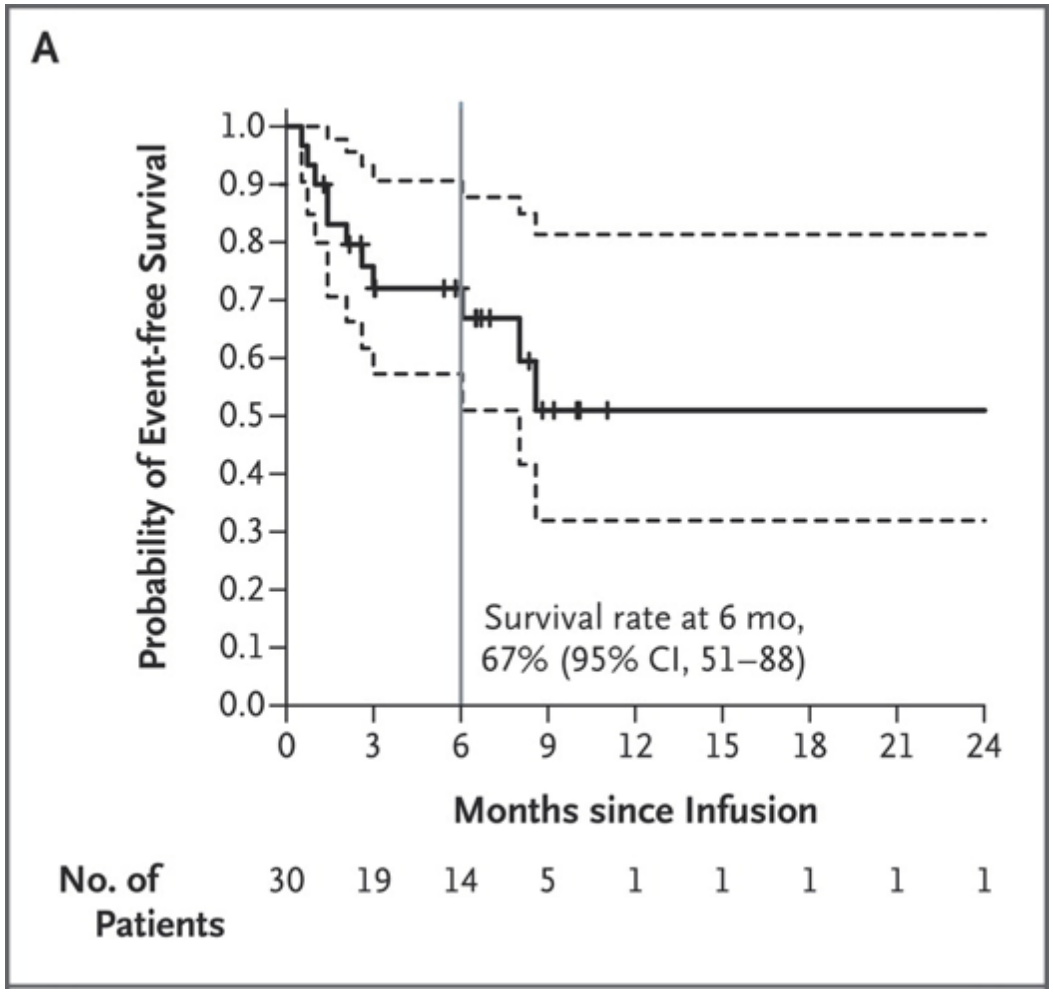


Image: labiotech.eu

The New York Times

Results of the CTL019 CART cells in B-ALL



30 adult and paediatric patients treated with CART

27 patients entered CR
All CR's associated with symptoms of CRS

6-month EFS of 67%
6-month OS of 78%

Maude et al, NEJM 2014

Results of CART trials in ALL

Table 1 | **CD19-specific-CAR T-cell therapy outcomes in patients with B-ALL**

Institution	CAR design	Patient population	Outcome	Toxicities	Reference
MSKCC	CD28, CD3ζ	• *n* = 32 adults • R/R B-ALL	91% CR	• B-cell aplasia • CRS	NCT01044069 (REF. 13)
UPenn/ CHOP	4-1BB, CD3ζ	• *n* = 30 children and young adults • B-ALL	90% CR	• B-cell aplasia • CRS	NCT01626495 (REF. 15)
NCI	CD28, CD3ζ	• *n* = 20 children and young adults • B-ALL	70% CR	• B-cell aplasia • CRS	NCT01593696 (REF. 17)
Fred Hutchinson	4-1BB, CD3ζ	• *n* = 20 adults • B-ALL	83% CR	CRS	NCT01865617 (REF. 18)

Preconditioning chemotherapy was used in all the trials shown in this table. B-ALL, B-cell acute lymphoblastic leukaemia; chemo, chemotherapy; CHOP, Children's Hospital of Philadelphia; CR, complete response; CRS, cytokine-release syndrome; Fred Hutchinson, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; R/R, relapsed and/or refractory; UPenn, The University of Pennsylvania.

Jackson, H. J. *et al.* (2016) Driving CAR T-cells forward
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.36

Summary of CD19 CAR T-Cell Efficacy in Relapsed/Refractory Adult ALL

CAR T-Cell Product	Median Age, Yrs (Range)	N	CAR T-Cell Dose	Efficacy
JCAR015 (19-28z)[1]	45 (22-74)	46	1 or 3 x 10^6 cells/kg	▪ CR, % • Overall: 82 • MRD neg: 83 • Ph pos: 93 • Ph neg: 77 ▪ Median OS, mos • Overall: 9.0 • MRD neg: NR • MRD pos: 6.0
CTL019 (19-4-1BBz)[2]	NA	12	NA	▪ CR: 89%
JCAR017 (19-4-1BBz)[3]	NA	20	2 x 10^5 to 2 x 10^7 cells/kg	▪ CR: 83%

1. Park JH, et al. ASH 2015. Abstract 682.
2. Frey NV, et al. ASH 2014. Abstract 2296.
3. Cameron JT, et al. ASCO 2015. Abstract 3006.

Ongoing Clinical Trials of CAR T Cells in Adult B-Cell ALL

- Single-arm, open-label, multicenter phase II study evaluating CTL019 in adults with relapsed/refractory B-cell ALL[1]
- ROCKET: single-arm, multicenter phase II study evaluating JCAR015 in adults with relapsed/refractory B-cell ALL[2]

1. ClinicalTrials.gov. NCT02167360.
2. ClinicalTrials.gov. NCT02535364.

19-28z CAR T Cells in R/R B-Cell ALL: Clinical Response

Response	Morphologic Disease (n = 30)	Minimal Disease (n = 20)
CR, %	77	90
MRD-negative CR, %	90 (n = 21)	78 (n = 18)
Mean time to CR, days (SD)	20 (9)	25 (9)

- CR seen across analyzed subgroups, including disease burden, prior blinatumomab, prior HSCT, number of prior therapies, Philadelphia chromosome status, and age
- 39% of pts achieving CR proceeded to allogeneic HSCT (equal incidence in morphologic and minimal disease cohorts)
- 45% MRD-negative CR pts relapsed; 27% of these were CD19 positive
- 27% MRD-negative CR pts disease free for > 1 yr

Park JH, et al. ASCO 2016. Abstract 7003.

19-28z CAR T Cells in R/R B-Cell ALL: OS

Response	Morphologic Disease (n = 31)	Minimal Disease (n = 20)
Median OS, mos	9.0	NR
Median OS in MRD-negative CR, mos	17.0	NR

- Median OS follow-up: 13.0 mos
- After CAR T cells, MRD negativity had prognostic implications
- Post–CAR T-cell HSCT does not appear to affect survival

Park JH, et al. ASCO 2016. Abstract 7003.

19-28z CAR T Cells in R/R B-Cell ALL: Conclusions

- CR and MRD-negative CR rates > 75% regardless of pretherapy disease burden[1]
- Durable responses and survival benefits in subset of patients without subsequent allogeneic HSCT (regardless of disease burden)
  - Benefit of allogeneic HSCT after 19-28z CAR T cells unclear
- Lower incidence of severe CRS and neurologic toxicities in pts with minimal disease burden prior to pre–T-cell infusion
- Single-arm phase II trial of 19-28z CAR T cells in R/R B-cell ALL ongoing (ROCKET)[2]

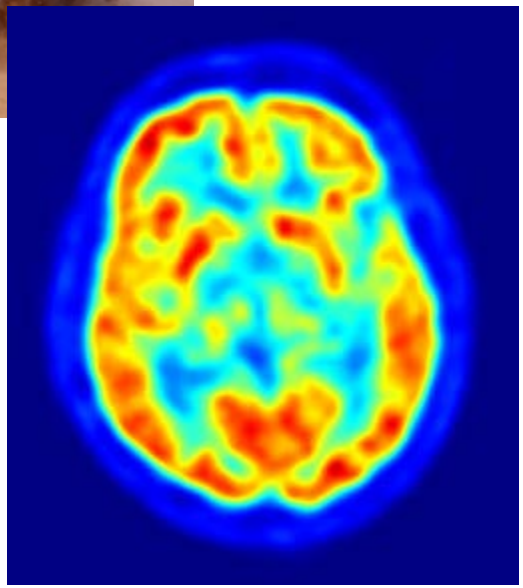
1. Park JH, et al. ASCO 2016. Abstract 7003.
2. ClinicalTrials.gov. NCT02535364.

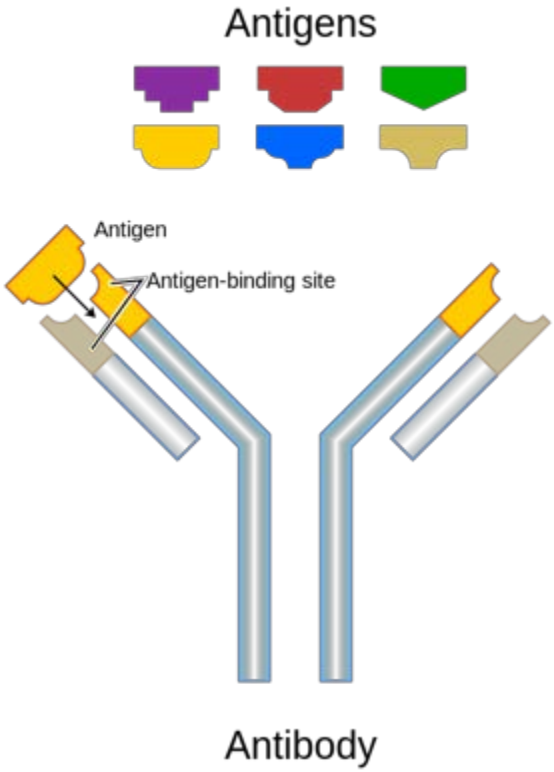
CTL019 in Adult ALL: Conclusions

- CTL019 dose and schedule correlate with response but also toxicity
- Fractionated (split) dosing allows for treatment modification to address CRS-related toxicity and maintain response
- CRS with concurrent sepsis portends poor prognosis
- Future studies needed to evaluate other dosing regimens and best timing for prophylactic and anticytokine therapy to minimize toxicity and optimize response

Frey NV, et al. ASCO 2016. Abstract 7002.

Toxicities of T-cell directed therapies in ALL





CART – is it a magic bullet?

- The results of CART studies are impressive, however several factors limit their broader application;
  - Patients need to have T-cells left
  - Cost
  - Time to produce CART cells
  - Risk of failure of product manufacture
  - Toxicities of CAR-T and lymphodepletion strategies.

Allogeneic CART

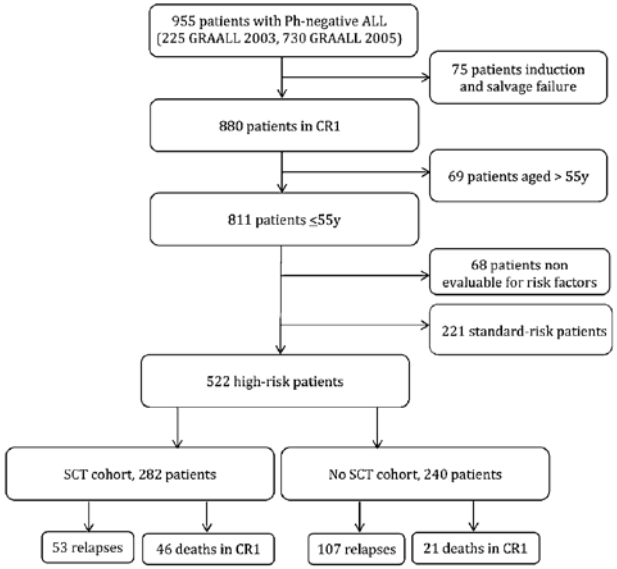
- Current CART trials have used autologous collected T-cells; allogeneic CART may provide an answer
  - Healthy donors have high T-cell levels
  - “Off the shelf” product
  - Mass production to drive down costs
- Potential risks
  - Alloimmunity – GVHD
  - Rejection

Murine allogeneic CD19 CAR T cells harbor potent antileukemic activity but have the potential to mediate lethal GVHD

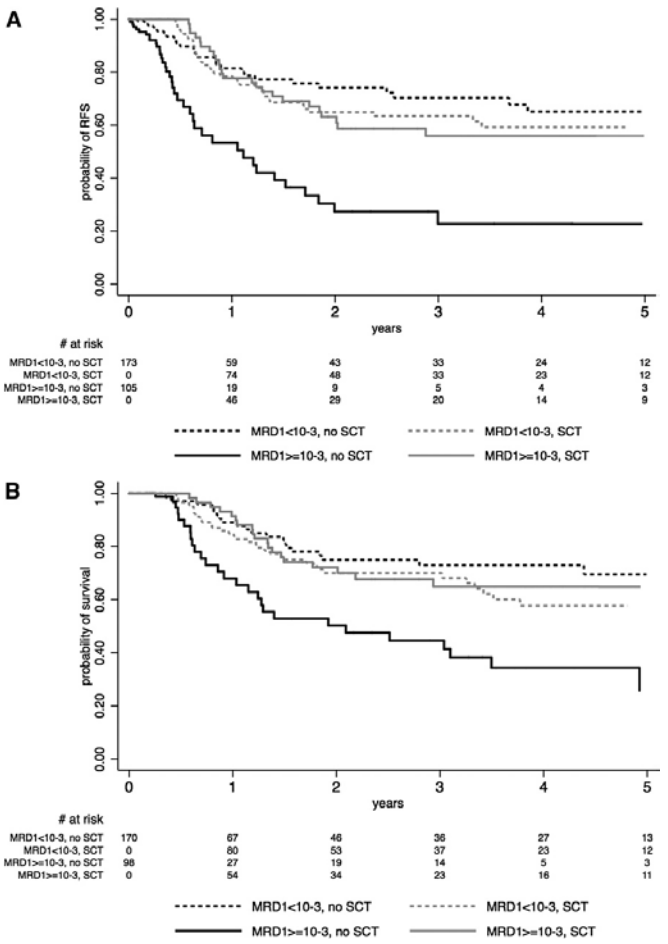
Elad Jacoby, Yinmeng Yang, Haiying Qin, Christopher D. Chien, James N. Kochenderfer, Terry J. Fry

Blood 2016 127:1361-1370; doi:10.1182/blood-2015-08-664250

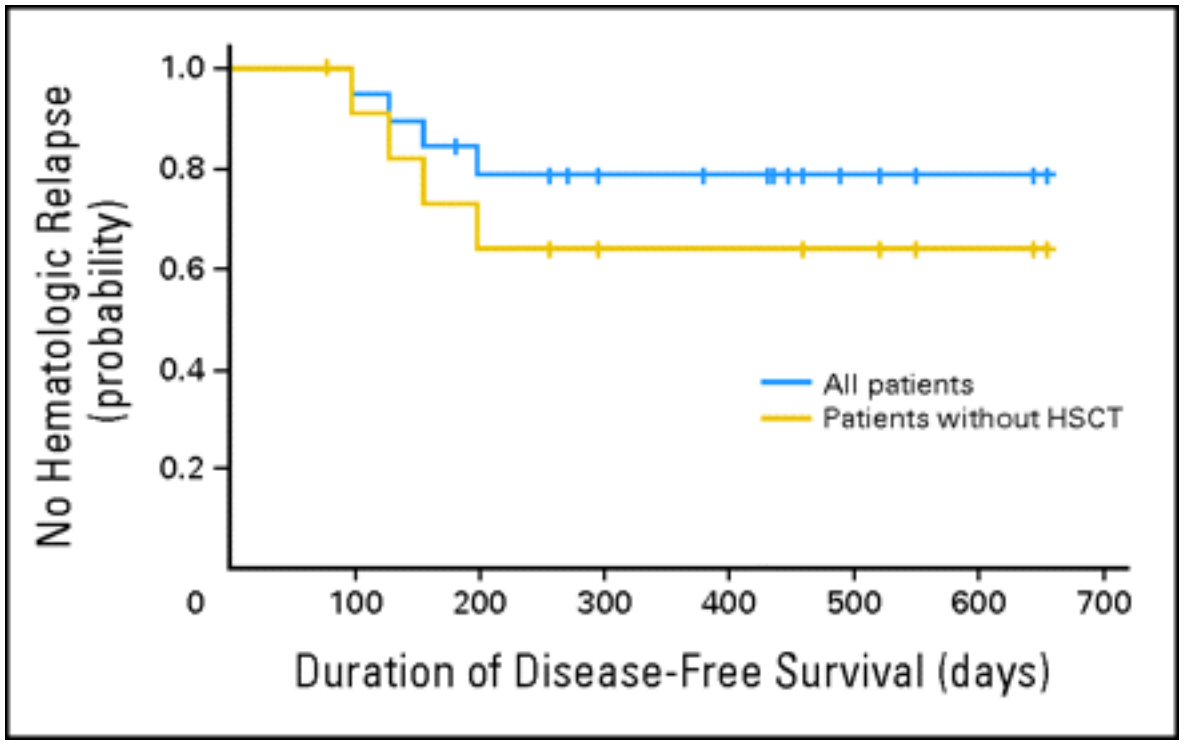
Minimal residual disease (MRD) is a major predictor of adverse outcome in ALL



Status	3-year RFS	3-year OS
MRD+ No Allo	55%	42%
MRD+ Allo	23%	65%
MRD- No Allo	70%	73%
MRD- Allo	62%	70%



Blinatumomab may lead to eradication of MRD in ALL – with durable responses



Topp et al, JCO 2011

Where are we at with Immunotherapy in ALL in 2017?

- Allogeneic transplantation remains the most effective immunotherapy for high-risk B-ALL
- Rituximab should now be considered standard of care in CD20+ B-ALL
  - The question about CD20- B-ALL remains unanswered
    - Steroids may drive up CD20 expression
    - Other effects of anti-CD20 antibodies
- Blinatumomab and Inotuzumab Ozogamicin should be considered as first salvage options for B-ALL
  - The decision between them is largely guided by toxicity profiles
- CART therapy offer an exciting prospect for the future in ALL
- Application of novel immunotherapies frontline, both in the unselected and MRD setting are the new therapeutic frontier as a potential bridge to (or alternative to) allogeneic transplant.